Scripps Research Institute-Designed Drug Candidate Significantly Reduces HIV Reactivation Rate

AIDS Study Points to 'Functional Cure'

July 8, 2015 – HIV-infected patients remain on antiretroviral therapy for life because the virus survives over the long-term in infected dormant cells. Interruption of current types of antiretroviral therapy results in a rebound of the virus and clinical progression to AIDS.

But now, scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown that, unlike other antiretroviral therapies, a natural compound called Cortistatin A reduces residual levels of virus from these infected dormant cells, establishing a near-permanent state of latency and greatly diminishing the virus’ capacity for reactivation.

“Our results highlight an alternative approach to current anti-HIV strategies,” said Susana Valente, a TSRI associate professor who led the study. “Prior treatment with Cortistatin A significantly inhibits and delays viral rebound in the absence of any drug. Our results suggest current antiretroviral regimens could be supplemented with a Tat inhibitor such as Cortistatin A to achieve a functional HIV-1 cure, reducing levels of the virus and preventing reactivation from latent reservoirs.”

The study was published this week in the journal *mBio*.

Cortistatin A was isolated from a marine sponge, *Corticium simplex*, in 2006, and in 2008, TSRI chemist Phil Baran won the global race to synthesize the compound. A configuration of the compound, didehydro-Cortistatin A, was shown in earlier studies to target the protein Tat, which exponentially increases viral production.

The new study shows that didehydro-Cortistatin A inhibits replication in HIV-infected cells by significantly reducing levels of viral messenger RNA – the blueprints for producing proteins and more infection.

“In latently infected primary T cells isolated from nine HIV-infected subjects being treated with antiretroviral drugs, didehydro-Cortistatin A reduced viral reactivation by an average of 92.3 percent,” said Guillaume Mousseau, the first author of the study and a member of the Valente lab.

The results suggest an alternative to a widely studied strategy for latent HIV eradication known as “kick and kill,” which tries to purge viral reservoirs by “kicking” them out of their latency with reversing agents and stopping new rounds of infection with an immunotherapy agent to boost the body’s own immune system response while on antiretroviral treatment.
“In our proposed model, didehydro-Cortistatin A inhibits the viral transcriptional activator, Tat, far more completely, delaying or even halting viral replication, reactivation and replenishment of the latent viral reservoir,” said Valente.

In addition to Valente and Mousseau, other authors of the study, “The Tat Inhibitor didehydro-Cortistatin A Prevents HIV-1 Reactivation from Latency,” include Cari F. Kessing of TSRI, and Rémi Fromentin, Lydie Trautmann and Nicolas Chomont formerly at the Vaccine and Gene Therapy Institute of Florida. See http://mbio.asm.org/content/6/4/e00465-15.abstract

This work was supported by the National Institutes of Health (grant R01AI097012) and by amfAR, a foundation for AIDS research (fellowship number 108264).

Scripps Florida Scientists Pinpoint Mechanism for Altered Pattern of Brain Growth in Autism Spectrum Disorder

July 15, 2015 – As early as 1943, when autism was first described by psychiatrist Leo Kanner, reports were made that some, but not all, children with autism spectrum disorder have relatively enlarged heads. But even today, more than half a century later, the exact cause of this early abnormal growth of the head and brain has remained unclear.

Now, scientists from the Florida campus of The Scripps Research Institute (TSRI) have uncovered how mutations in a specific autism risk gene alter the basic trajectory of early brain development in animal models.

The study, published in the July 15 issue of The Journal of Neuroscience, focused on the gene PTEN (Phosphatase and tensin homolog), which is mutated in around 20 percent of individuals with autism spectrum disorder and enlarged heads (macrocephaly).

In new research, the team led by Scripps Florida biologist Damon Page found that mutations in the mouse version of PTEN, which approximate those found in a subgroup of individuals with autism spectrum disorder, lead to dynamic changes in the number of two key cell types that make up the brain—neurons and glia. At birth, neurons are more abundant than normal. Surprisingly, in adulthood the number of neurons in the brains of mutant animals is virtually the same as normal, and glia (which provide support for neurons) are overrepresented.

“In the adult brain, excess glia are a primary cause of the overall change in brain size,” Page said. “This raises the intriguing possibility that these excess glia may, in fact, contribute to abnormal development and function of brain circuitry when PTEN is mutated.”

The brain overgrowth the team observed in PTEN mutant mice is a dynamic process, with the greatest increase in size occurring at birth and adulthood and the least in the early juvenile period. The team noted that this abnormal pattern of growth appears to be caused by an amplification of the normal process of brain development, where neurons are generated in over-abundance before birth and then trimmed off by a program of cell death (apoptosis), and glia are generated after neurons.
“Apoptosis is a natural phenomenon that removes unnecessary neurons during normal brain development,” said Research Associate Youjun Chen, the first author of the study and a member of the Page laboratory. “We find it very striking that in the brains of PTEN mutant mice, the presence of excess neurons is corrected by excessive apoptosis. After that, excess glia are made. In adulthood, the number of glial cells increases by more than 20 percent in our models.”

The scientists traced these effects back to an increase in signaling through a molecule known as β-Catenin (beta Catenin).

“PTEN and β-catenin are two important molecules that control growth in the developing brain in both mice and humans,” said Page. “We have found that these work together in a common pathway to regulate brain growth trajectory by controlling the number and types of cells produced. Although caveats apply when extrapolating from mice to humans, this suggests that an imbalance in this relationship may contribute to abnormal brain growth in a subset of individuals with autism spectrum disorder.”

Autism spectrum disorder is a neurodevelopmental disorder characterized by social deficits and communication difficulties, repetitive behaviors and interests, as well as cognitive delays in some individuals. The disorder affects in approximately one percent of the population; some 80 percent of those diagnosed are male.

Interestingly, Page noted that in spite of the profound effects of PTEN mutations on brain growth, the mice are largely able to adapt at the level of behavior, with the important exception of social behavior and a few other behaviors relevant to autism spectrum disorder.

“Our findings across studies indicate that it may be a multiple-hit process,” he said. “While abnormal growth puts stress on the developing brain, the brain works hard to compensate for that. How well an individual can adapt to an abnormal pattern of brain growth may shape their outcome in terms of behavior and cognition. The capacity to adapt may, in turn, be influenced by genetic or environmental factors.”

In addition to Page and Chen, other authors of the study, “Pten Mutations Alter Brain Growth Trajectory and Allocation of Cell Types through Elevated β-Catenin Signaling,” are Wen-Chin Huang, Julien Sejourne and Amy E. Clipperton-Allen of TSRI.

This work was supported by the state of Florida, Ms. Nancy Lurie Marks, the Simons Foundation (grant award 360712), an O’Keeffe Neuroscience Scholars Award and the Fraternal Order of Eagles.

**Scripps Florida Scientists Receive $2.8 Million to Develop Innovative Approach to Latent HIV Infection**

July 16, 2015 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have been awarded a pair of grants totaling nearly $2.8 million from the National Institute of
Allergy and Infectious Diseases of The National Institutes of Health to develop a new therapeutic agent to reduce latent levels of HIV that hide from the immune system in infected individuals.

TSRI Associate Professor Susana Valente will be the principal investigator of the multiyear grants.

“Our approach is aimed at a novel antiviral target, a protein known as a potent activator of HIV gene expression,” Valente said. “With this new funding, we can continue to develop our approach to the difficult problem of HIV latency, finding a way to suppress the virus in these latently infected cells.”

Valente’s research is focused on blocking the Tat protein, which is essential for viral amplification.

In the new project, Valente’s team will explore the potential of didehydro-Cortistatin A (dCA), a molecule closely related to a natural compound isolated from a marine sponge, to reduce the size of the latent reservoir pool of HIV by blocking ongoing viral replication, reactivation and replenishment.

“The new grant will help us confirm didehydro-Cortistatin A as workable inhibitor and better understand the mechanism of viral resistance to it,” Valente said.

The numbers of the grants are 1R21AI112462 and 1R01AI118432.

**Scripps Florida Scientists Win $1.5 Million to Study New Strategies for Parkinson’s Disease and Other Disorders**

July 27, 2015 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have been awarded nearly $1.5 million from the National Institute of General Medical Sciences of the National Institutes of Health to explore the therapeutic potential of a class of proteins that play essential roles in the regulation and maintenance of human health.

These proteins are expressed throughout the body, including the central nervous system during brain development, and are associated with conditions including Parkinson’s disease, inflammation, arthritis, cancer, metabolic disorders (dyslipidemia, obesity, diabetes) and cardiovascular disease.

“These protein receptors have not been well studied, particularly in terms of small-molecule compounds that could affect their function,” said TSRI Associate Professor Douglas Kojetin, who is the principal investigator of the new four-year study. “We’ve found several natural small-molecule binding partners for a particular orphan receptor called Nurr1. It’s called an orphan receptor because natural small-molecule binding partners for this receptor are currently unknown, and this new grant will help uncover important details of the process. This study will potentially open up an entire new class of compounds that could affect millions of people with crippling diseases such as Parkinson’s.”
Kojetin’s laboratory focuses on the mode of action of small-molecule ligands (molecules that bind to other molecules and alter their function). In particular, the team studies how these ligands change the structure and dynamics of the proteins they target and how this contributes to biological function, disease and drug discovery.

The number of the grant is 1R01GM114420.

**Scripps Florida Scientists Receive $1.4 Million to Study Drug Candidates for Neurological Disorders and Other Diseases**

July 28, 2015 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have been awarded $1.4 million from the National Institute of Mental Health of the National Institutes of Health (NIH) to explore the development of drug candidates for a wide range of conditions, including circadian rhythm disorders.

Patrick R. Griffin, chair of the Department of Molecular Therapeutics at Scripps Florida, and Theodore Kamenecka, a TSRI associate professor, will be the principal investigators of the new three-year grant.

The project involves what are known as RORs (retinoic acid receptor-related orphan receptors), a class of molecules that plays a role in the expression of genes involved in carbohydrate and fat metabolism, inflammation and circadian rhythm. Disruptions in circadian rhythm—the pattern of activity and rest over a 24-hour daily cycle—have been associated with depression, bipolar disease and schizophrenia.

“While the functions of other ROR receptors have been widely studied, little is known about RORbeta,” Griffin said. “The new grant will allow us to expand and improve our experimental compounds to study RORbeta function in depth. This line of research should increase our understanding of this receptor as well as circadian rhythm and related disorders.”

While not specifically aimed at producing drug candidates, Griffin said, the new research will include studies of the new optimized compounds in experimental models of a range of diseases.

The number of the grant is 1R01MH108173.

**Scripps Florida Scientists Make Strides in Therapy Preventing Addiction Relapse by Erasing Drug-Associated Memories**

*Single Injection of Drug Candidate Prevents Meth Relapse in Animal Models*

August 4, 2015 – Recovering addicts often grapple with the ghosts of their addiction—memories that tempt them to relapse even after rehabilitation and months, or even years, of drug-free living. Now, scientists from the Florida campus of The Scripps Research Institute (TSRI) have made a discovery that brings them closer to a new therapy based on selectively erasing these dangerous and tenacious drug-associated memories.
“We now have a viable target and by blocking that target, we can disrupt, and potentially erase, drug memories, leaving other memories intact,” said TSRI Associate Professor Courtney Miller. “The hope is that, when combined with traditional rehabilitation and abstinence therapies, we can reduce or eliminate relapse for meth users after a single treatment by taking away the power of an individual’s triggers.”

The new study, published this week online ahead of print by the journal Molecular Psychiatry, demonstrates the effectiveness of a single injection of an early drug candidate called blebbistatin in preventing relapse in animal models of methamphetamine addiction.

The new study builds on previous work in Miller’s lab. In 2013, the team made the surprising discovery that drug-associated memories could be selectively erased by targeting actin, the protein that provides the structural scaffold supporting memories in the brain. However, the therapeutic potential of the finding seemed limited by the problem that actin is critically important throughout the body—taking a pill that generally inhibits actin, even once, would likely be fatal.

In the new study, Miller and her colleagues report a major advance—the discovery of a safe route to selectively targeting brain actin through nonmuscle myosin II (NMII), a molecular motor that supports memory formation. To accomplish this, the research used a compound called blebbistatin that acts on this protein.

The results showed that a single injection of blebbistatin successfully disrupted long-term storage of drug-related memories—and blocked relapse for at least a month in animal models of methamphetamine addiction.

“What makes myosin II such an exciting therapeutic target is that a single injection of blebbistatin makes methamphetamine-associated memories go away, along with dendritic spines, the structures in the brain that store memory,” said Research Associate Erica Young, a member of the Miller lab and a key author of the new study, along with Research Associates Ashley M. Blouin and Sherri B. Briggs.

Blouin added, “Drugs targeting actin usually have to be delivered directly into the brain. But blebbistatin reaches the brain even when injected into the body’s periphery and, importantly, the animals remained healthy.”

Moreover, the effect of this novel treatment approach was specific to drug-associated memories (not affecting other memories), and the animals were still able to form new recollections. “Our results argue for developing small molecule inhibitors of nonmuscle myosin II as potential therapeutics for relapse prevention, and that’s exactly what we’re doing with our colleagues here at Scripps with expertise in drug development,” said Briggs.

In addition to Miller, Young, Blouin and Briggs, other authors of the study, “Nonmuscle Myosin IIB as a Therapeutic Target for the Prevention of Relapse to Methamphetamine Use,” include Stephanie E. Sillivan, Michael D. Cameron and Gavin Rumbaugh of TSRI.
Scripps Florida Scientists Show How Aging Cripples the Immune System, Suggesting Benefits of Antioxidants

August 6, 2015 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown how aging cripples the production of new immune cells, decreasing the immune system’s response to vaccines and putting the elderly at risk of infection. The study goes on to show that antioxidants in the diet slow this damaging process.

The research, published August 6 in the journal *Cell Reports*, focused on an organ called the thymus, which produces T lymphocytes, critical immune cells that must be continuously replenished to respond to new infections.

“The thymus begins to atrophy rapidly in very early adulthood, simultaneously losing its function,” said TSRI Professor Howard Petrie. “This new study shows for the first time a mechanism for the long-suspected connection between normal immune function and antioxidants.”

Scientists have been hampered in their efforts to develop specific immune therapies for the elderly by a lack of knowledge of the underlying mechanisms of this process.

To explore these mechanisms, Dr. Petrie and his team developed a computational approach for analyzing the activity of genes in two major thymic cell types—stromal cells and lymphoid cells—in mouse tissues, which are similar to human tissues in terms of function and age-related atrophy. The team found that stromal cells were specifically deficient in an antioxidant enzyme called catalase, which resulted in elevated levels of the reactive oxygen by-products of metabolism and, subsequently, accelerated metabolic damage.

To confirm the central role of catalase, the scientists increased levels of this enzyme in genetically altered animal models, resulting in preservation of thymus size for a much longer period. In addition, animals that were given two common dietary antioxidants, including vitamin C, were also protected from the effects of aging on the thymus.

Taken together, the findings provide support for the “free-radical theory” of aging, which proposes that reactive oxygen species such as hydrogen peroxide, produced during normal metabolism, cause cellular damage that contributes to aging and age-related diseases.

While other studies have suggested that sex hormones, particularly androgens such as testosterone, play a major role in the aging process, they’ve failed to answer the key question—why does the thymus atrophy so much more rapidly than other body tissues?
“There’s no question that the thymus is remarkably responsive to androgens,” Dr. Petrie noted, “but our study shows that the fundamental mechanism of aging in the thymus, namely accumulated metabolic damage, is the same as in other body tissues. However, the process is accelerated in the thymus by a deficiency in the essential protective effects of catalase, which is found at higher levels in almost all other body tissues.”

The first author of the study, “Metabolic Damage and Premature Thymus Aging Caused by Stromal Catalase Deficiency,” is Ann V Griffith, currently on the faculty of the University of Texas and working at TSRI at the time of the study. Other authors include Jianjun Shi and Mohammad Fallahi of TSRI; Andrew Farr and Peter Rabinovitch of the University of Washington; and Holly van Remmen and Luke Szweda of the Oklahoma Medical Research Foundation.

This work was supported by U.S. Public Health Service (grants AG031576 and AI103340).

**Scripps Florida Scientists Determine How Antibiotic Gains Cancer-Killing Sulfur Atoms**

August 10, 2015 – In a discovery with implications for future drug design, scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown an unprecedented mechanism for how a natural antibiotic with antitumor properties incorporates sulfur into its molecular structure, an essential ingredient of its antitumor activity.

This new discovery could open the way to incorporating sulfur into other natural products, potentially advancing new therapies for indications beyond cancer.

The study, which was led by TSRI Professor Ben Shen, was recently released online ahead of print by the journal *Proceedings of the National Academy of Sciences, USA*.

“We found a novel mechanism to incorporate sulfur into natural products, which is unprecedented,” Shen said. “Until our study, we didn’t really know how sulfur atoms are incorporated into a natural product—now we have discovered a new family of enzymes and have a workable mechanism to account for sulfur incorporation into a larger class of natural products, known as polyketides, that include many drugs such as erythromycin (antibacterial) and lovastatin (cholesterol lowering).”

Sulfur is critical not only to human life, but to plants and bacteria as well, and is one of the most abundant elements in the human body by weight. A number of compounds that contain sulfur have proven useful in the treatment of conditions ranging from acne and eczema to arthritis and cancer.

The new study is focused on leinamycin (LNM), a sulfur-containing antitumor antibiotic produced by species of the soil-dwelling bacterium *Streptomyces*. The Shen laboratory has been studying the potential of this natural compound for development of anticancer drugs. They recently reported the discovery of LNM E1, an engineered analogue of LNM, as a “prodrug,” a
medication converted through a metabolic process in the body to become an active therapy (see “Scripps Florida Scientists Show Antitumor Agent Can Be Activated by Natural Response to Cell Stress”).

“With LNM, sulfur plays the critical role in its anticancer activity,” Shen said. “With many other natural products, sulfur could add other therapeutic properties. This is the beauty of fundamental research—it lays the foundation to create novel technologies that enable innovative translational research with implications far beyond the original discovery.”

The study links a family of enzymes—molecules that act as biological catalysts—known as polyketide synthases (PKS) directly to a complex series of chemical reactions that ultimately add sulfur to leinamycin, a member of the polyketide family of natural products.

“The sulfur incorporation mechanism discovered in our study revealed the novel function of a polyketide synthase, greatly expanding our understanding of its chemistry,” said TSRI's Ming Ma, a co-first author of the study with Jeremy R. Lohman of TSRI and Tao Liu of the University of Wisconsin, current and former members of the Shen lab. “Since polyketide synthases are a large family of enzymes that have been proven amenable for polyketide structural diversity and drug discovery, it is particularly exciting that this new discovery now provides the possibilities of adding sulfur atoms to compounds similar to leinamycin or other polyketide natural products.”

Because few sulfur-containing natural products are known, this particular enzyme and its gene could now be useful tools to probe ecological niches for the discovery of other sulfur-containing natural products.

For more information on the study, “C-S Bond Cleavage by a Polyketide Synthase Domain,” see http://www.pnas.org/content/early/2015/07/30/1508437112.abstract?sid=ec97607b-cc2c-4d81-bf84-f1200e83f5a6

This work was supported by the National Institutes of Health (grant CA106150).

Scripps Florida Scientists Collaborate to Determine First Structure of Crucial Plant Hormone

August 11, 2015 – An international collaboration including scientists from the Florida campus of The Scripps Research Institute (TSRI) has determined the structure of a plant hormone that plays a crucial role in regulating plants’ responses to insects and disease-causing microorganisms as well as normal growth and development.

The new study, published by the journal *Nature*, focused on a plant hormone called jasmonate and two proteins involved in its molecular signaling, MYC and JAZ.

Previous attempts to determine a three-dimensional picture of this interaction were frustrated when scientists had great difficulties forming crystals of MYC and JAZ bound to one another—a
necessary step to determine molecular structure using a high-resolution technique called x-ray crystallography.

“The outstanding question answered in the study is why the protein complex crystallization between MYC and the JAZ motif was so difficult, given the binding affinity is so tight,” said Patrick R. Griffin, chair of the Department of Molecular Therapeutics and director of the Translational Research Institute at Scripps Florida. “As a collaborative effort, the study revealed structural intricacies in the MYC factor that are highly flexible.”

The study included scientists from Michigan State University, Howard Hughes Medical Institute (HHMI), the Chinese Academy of Sciences, Zhejiang Sci-Tech University, Nanjing Agricultural University, Van Andel Research Institute, Western Michigan University and Northwestern University.

Griffin’s laboratory contributed to the study with its leading-edge expertise in HDX (short for hydrogen-deuterium exchange mass spectrometry), an advanced method of examining alterations in the dynamics of proteins and how these changes relate to protein function. With the help of HDX, the team was able to show that the structural conformation of the MYC factors changes profoundly when bound to one of the JAZ repressors. This key finding led to the making of a JAZ-MYC fusion construct, resulting in high quality crystals.

“Although the solved crystal structure of the MYC transcription factor in question only captured a snapshot of a favored conformation, it does explain nicely how the JAZ acts as a dual repressor/activator switch to the MYC,” said Vinh Q. Lam, a senior research associate in the Griffin lab who worked on the study. “The HDX studies indicate that, in solution, the regions occupied by JAZ are highly dynamic.”

Whether this flexibility is required for downstream function is not yet clear. Thus, future studies will include multiple components in experiments to elucidate the jasmonate signaling pathway.

In addition to Griffin and Lam, other authors of the study, “Structural Basis of JAZ Repression of MYC Transcription Factors in Jasmonate Signaling,” include corresponding author Sheng Yang He of Michigan State University and HHMI; first authors Feng Zhang and Jiyan Ke of the Van Andel Research Institute and Jian Yao of Michigan State; Li Zhang and Xiu-Fang Xin of Michigan State; X. Edward Zhou, Jian Chen, H. Eric Xu and Karsten Melcher of Van Andel Research Institute and the Chinese Academy of Sciences; Joseph Brunzelle of Northwestern University; and Mingguo Zhou of Nanjing Agricultural University. See http://www.nature.com/nature/journal/vaop/ncurrent/full/nature14661.html

This research was supported by the Gordon and Betty Moore Foundation (GBMF3037), the China Scholarship Council, Van Andel Research Institute, the National Institutes of Health (R01 GM102545 and R01AI060761), U.S. Department of Energy (grant DE–FG02–91ER20021, contract DE-AC02-06CH11357), Michigan Economic Development Corporation and the Michigan Technology Tri-Corridor (grant 085P1000817).
Scripps Florida Scientists’ Structural Discoveries Could Aid in Better Drug Design

August 25, 2015 – F. Scott Fitzgerald once said that the test of a first-rate intelligence is the ability to hold two opposed ideas in mind at the same time and still retain the ability to function. Now, scientists from the Florida campus of The Scripps Research Institute (TSRI) have found the biological equivalent of that idea or something very close.

For the first time, they have uncovered the structural details of how some proteins interact to turn two different signals into a single integrated output. These new findings could aid future drug design by giving scientists an edge in fine tuning the signal between these partnered proteins—and the drug’s course of action.

“Thyroid, vitamin D and retinoid receptors all rely on integrated signals—their own signal plus a partner receptor,” said TSRI Associate Professor Kendall Nettles, who led the study with TSRI colleague Associate Professor Douglas Kojetin. “These new findings will have important implications for drug design by clearly defining exactly how these signals become integrated, so we will be able to predict how changes in a drug’s design could affect signaling.”

The study was published recently in the journal Nature Communications.

Using a number of complementary technologies, including nuclear magnetic resonance (NMR), X-ray crystallography and hydrogen/deuterium exchange (HDX) mass spectrometry from the laboratory of Scripps Florida colleague Chair of the Department of Molecular Therapeutics Patrick R. Griffin, the scientists were able to determine the mechanism through which two signaling pathways become integrated.

The study focused on a small subset of nuclear receptors, a large family of proteins that regulate gene expression in response to signals from various binding partners, including steroids and fats. Once receptors sense the presence of these binding partners, they send out new signals that initiate other cellular processes.

“Nuclear receptors bind different types of molecules, and some of these receptors physically interact with each other to integrate different signals,” Kojetin said. “Earlier studies basically accepted this without any structural evidence for communication between receptors. This is the first time that anyone has looked at what’s actually going on at the atomic level.”

In addition to Nettles, Kojetin and Griffin, authors of the study, “Structural Mechanism for Signal Transduction in RXR Nuclear Receptor Heterodimers,” include Edna Matta-Camacho, Travis S. Hughes, Sathish Srinivasan, Jerome C. Nwachukwu, Valerie Cavett, Jason Nowak, Michael J. Chalmers, David P. Marciano and Theodore M. Kamenecka of TSRI; Andrew I. Shulman of the University of California, Irvine; Mark Rance of the University of Cincinnati; and John B. Bruning of The University of Adelaide. See http://www.nature.com/ncomms/2015/150820/ncomms9013/full/ncomms9013.html
The work was supported by the National Institutes of Health (grants DK101871, GM114420, GM063855, RR019077, RR027755, MH084512, GM084041, RR027270 and CA132022), the Frenchman’s Creek Women for Cancer Research, the James and Esther King Biomedical Research Program, the Florida Department of Health and the State of Florida.

Scripps Florida Scientists Identify a Key Morphine Regulator that May Reduce Risk of Pain-Killer Abuse and Addiction

September 22, 2015 – Once used in the 18th century as currency to reverse the trade imbalance between China and Britain, morphine and its pain-killing qualities have been misunderstood (and misused) almost continually ever since.

The drug works its euphoric effect by acting on a specific protein that has been part of vertebrate anatomy for nearly a half-billion years. Despite that lengthy pedigree, regulation of these receptor proteins has never been well understood.

A new study led by Kirill Martemyanov, an associate professor on the Florida campus of The Scripps Research Institute (TSRI), has shown that a specific molecule controls morphine receptor signaling in a small group of brain cells. The findings could lead to a new drug target for developing less-addictive pain medications and even offer a clue to the genetic predisposition of patients to addiction before treatment.

The study was published recently online ahead of print by the journal *Biological Psychiatry*.

The molecule in question is known as a regulator of G protein signaling (RGS) protein, which controls the morphine receptor (mu opioid receptor). Using genetically modified animal models lacking a particular RGS protein called RGS7, a protein abundant in the brain, the study showed that eliminating the protein enhanced reward, increased pain relief, delayed tolerance and heightened withdrawal in response to self-administered morphine doses. In other words, without the protein, the animals were predisposed to morphine addiction.

“The mu opioid receptor acts as a conductor of the drug’s effects, while RGS7 acts as a brake on the signal,” Martemyanov said. “The animals could press a lever to receive an infusion of morphine. We looked at the number of lever presses to determine how much they liked it and, judging from this test, mice lacking RGS7 craved the drug much more than their normal siblings.”

RGS7 appears to exert its effects by regulating morphine-induced changes in excitability of neurons and plasticity of synapses—the ability of the synapse, the junction between two nerve cells, to change its function.

“This study reveals a unique modulatory role of RGS7 in a brain-region-specific action to morphine use and indicates RGS7 as a potential drug target,” said Research Associate Laurie P. Sutton, the first author of the study. “Pharmacological intervention at the level of RGS7 may reduce some of the detrimental side-effects associated with opiates.”
Martemyanov believes there is a strong diagnostic future for their discovery. “If our findings hold true for human patients, you could look specifically for RGS7 levels for any disabling mutation with a simple blood test,” he said. “Mutations could indicate a strong reaction to a drug such as morphine—people carrying a deficient copy of the RGS7 gene might need much lower doses of opioids and could be cautioned to be extra careful with these substances.”

This might also shed light on why some people have such a difficult time with addiction to drugs such as morphine, while others are not so susceptible, Martemyanov noted.

Surprisingly, in addition to drug craving, the animals lacking RGS7 also worked harder to obtain a food reward, further suggesting that RGS7 may be a more general regulator of reward behavior extending beyond drug-induced euphoria.

In addition to Sutton and Martemyanov, other authors of the study, “RGS7 Regulates Reward Behavior by Controlling Opioid Signaling in the Striatum,” were Olga Ostrovskaya, Maria Dao, Keqiang Xie, Cesare Orlandi, Roy Smith and Sunmee Wee, all of TSRI at the time of the study. For more information, see [http://www.biologicalpsychiatryjournal.com/article/S0006-3223(15)00653-8/abstract](http://www.biologicalpsychiatryjournal.com/article/S0006-3223(15)00653-8/abstract)

This work was supported by the National Institutes of Health (grants DA026405, DA036082 and DA036596) and the Canadian Institutes of Health.

**Scripps Florida Scientists Awarded $6 Million to Develop Alternative HIV/AIDS Vaccine**

September 23, 2015 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have been awarded up to nearly $6 million from the Bill & Melinda Gates Foundation to develop a revolutionary HIV/AIDS alternative vaccine that has demonstrated great potential in animal models.

The research, to be led by TSRI Professor Michael Farzan, will be supported by four years of funding—the first grant awarded by the Gates Foundation to a Scripps Florida scientist.

“I’m grateful to the Gates Foundation for its strong support of our research and for its continued commitment to eradicating HIV/AIDS throughout the world,” Farzan said.

Farzan brings an innovative approach to combating HIV. The approach works by coaxing muscle cells into producing inhibitor proteins that block key sites on the virus’s surface used to attach and invade human immune cells—fooling the virus into thinking it is binding to a human cell. Unable to attach to cells, and unable to reproduce, the virus simply floats impotently in the bloodstream.

Farzan and colleagues’ breakthrough research received worldwide attention when announced earlier this year in the journal *Nature*. When the drug candidate, called eCD4-lg, was tested in the laboratory and in animal models, the results were so powerful and universally effective that
they suggested the compound’s potential to serve the role of an alternative HIV/AIDS vaccine. The drug candidate offered complete protection of animal models against the virus for up to one year.

“Our compound eCD4-Ig is the broadest and most potent entry inhibitor described so far, effective against all strains tested,” Farzan said. “At the end of our research, we expect to have enough evidence to develop a firm foundation to fully evaluate its potential as an alternative vaccine.”

There are approximately 35 million people living with HIV-1—more than 25 million in sub-Saharan Africa—and more than two million new infections annually.

Scripps Florida Scientists Identify Promising Drug Candidate to Treat Chronic Itch that Avoids Side Effects

September 28, 2015 – If you have an itch, you have to scratch it. But that’s a problem for people with a condition called “chronic intractable itch,” where that itchy sensation never goes away—a difficult-to-treat condition closely associated with dialysis and renal failure.

In a new study, scientists from the Florida campus of The Scripps Research Institute (TSRI) describe a class of compounds with the potential to stop chronic itch without the adverse side effects normally associated with medicating the condition.

“Our lab has been working on compounds that preserve the good properties of opioids and eliminate many of the side effects,” said TSRI Professor Laura Bohn. “The new paper describes how we have refined an aspect of signaling underlying how the drugs work at the receptor so they still suppress itch and do not induce sedation. Developing compounds that activate the receptors in this way may serve as a means to improve their therapeutic potential.”

The study, which was published recently in the journal Neuropharmacology, used a compound called isoquinolinone 2.1 to target the kappa opioid receptor, which is widely expressed in the central nervous system and serves to moderate pain perception and stress responses.

The compound was effective in stopping irritant-induced itch, without causing sedation, in mouse models of the condition.

Bohn noted isoquinolinone 2.1 is one example of a new class of “biased” kappa agonists that avoid many central nervous system side effects by preferentially activating a G protein-mediated signaling cascade without involving another system based on β-arrestin protein interactions.

The first author of the study, “Investigation of the Role of Beta Arrestin2 in Kappa Opioid Receptor Modulation in a Mouse Model of Pruritus,” was Jenny Morgenweck. Other authors include Kevin J. Frankowski, Thomas E. Prisinzano and Jeffrey Aubé of The University of Kansas and the University of North Carolina-Chapel Hill. See http://www.sciencedirect.com/science/article/pii/S0028390815300721
The work was supported by the National Institutes of Health’s National Institute on Drug Abuse (grant R01DA031927).

**Scripps Florida Scientists Identify Key Neurotransmitter Receptor as Potential Target for Individualized Treatment of Autism Spectrum Disorder**

*Grant of $2.4 Million Will Support Further Research*

September 30, 2015 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have uncovered a significant—and potentially treatable—relationship between a chemical that helps transmit signals in the brain and genetic mutations present in a subset of individuals with autism spectrum disorder.

The new research findings, which were published recently in the journal PLoS One, focus on the role that the neurotransmitter serotonin plays in the development of social behavior. Serotonin, together with the serotonin receptors it activates in the brain, plays a significant role in neurological processes, including mood, anxiety, aggression and memory.

The study made use of an animal model of mutations in the gene *Pten*, a risk factor present in a subgroup of individuals with autism. Treatment of this model with a drug that suppresses the activity of a particular serotonin receptor, 5-HT2cR, can have a dramatic effect.

“Our research shows that targeting one specific serotonin receptor can reverse social deficits in a mouse model of the autism risk gene *Pten,*” said Julien Séjourné, the first author of the new study. “This discovery is important for understanding the role of this specific subtype of serotonin receptor in autism-relevant behaviors and could lead to new therapeutic strategies.”

“We found a striking contrast between the effects of dialing down the activity of the receptor using a drug, which improved social deficits in the *Pten* model, versus removing the receptor completely by mutation, which actually impaired social behavior,” added TSRI Assistant Professor Damon Page, who led the study. “Important issues will be uncovering the mechanism by which modulating serotonin receptor activity can influence autism-relevant symptoms and identifying the time window and dose range where targeting serotonin receptors is most effective.”

Page was recently awarded a $2.4 million, five-year grant from the National Institute of Mental Health of The National Institutes of Health (NIH) to further study the relationship between abnormal patterns of brain growth, neurotransmitter signaling and the behavioral and cognitive symptoms in individuals with autism spectrum disorder.

“The new grant will let us expand our research into the relationship between specific risk factors, altered brain development and key neurotransmitter systems, with the ultimate goal of moving toward individualized treatments for particular subgroups of individuals with autism spectrum disorder,” he said.
In addition to Page and Séjourné, other authors of the study, “Social Behavioral Deficits Coincide with the Onset of Seizure Susceptibility in Mice Lacking Serotonin Receptor 2c,” are Danielle Llaneza of TSRI and Orsolya J. Kuti of The Massachusetts Institute of Technology. See http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0136494

The work was supported by Ms. Nancy Lurie Marks and the National Institutes of Health. The number of the grant is 1R01MH105610.

**Scripps Florida Scientist Wins Coveted National Institutes of Health Pioneer Award**

October 6, 2015 – Matthew D. Disney, a professor on the Florida campus of The Scripps Research Institute (TSRI) has been awarded a prestigious 2015 Pioneer Award from the National Institutes of Health (NIH). The award, one of only 13 given this year, enables scientists to develop groundbreaking approaches with a significant impact on broad areas of biomedical science.

“This program has consistently produced research that revolutionized scientific fields by giving investigators the freedom to take risks and explore potentially groundbreaking concepts,” said NIH Director Francis S. Collins. “We look forward to the remarkable advances in biomedical research the 2015 awardees will make.”

“This is a great honor not only for Matt and his lab, but for The Scripps Research Institute as well,” said TSRI’s President-Elect Steve Kay. “Matt’s work represents the kind of research the institute is known for—bold, imaginative and aimed at helping those people with the greatest medical needs. Our congratulations to Matt on this well-deserved achievement.”

Dale Boger, chair of TSRI’s Department of Chemistry, added, “We are thrilled to learn that Professor Disney’s work has been recognized and funded with a coveted NIH Pioneer Award. His research addresses fundamental questions on targeting RNA with therapeutics and has resulted in exciting translational opportunities.”

The Pioneer Award, established in 2004, is part of the NIH’s High-Risk, High-Reward Research program supported by the NIH Common Fund. Disney’s Pioneer Award provides $4.8 million of funding over five years.

“We will use the money wisely to advance precision therapeutics that trick disease-affected cells into making their own drug against diseases for which there are no known cures,” said Disney. “I am honored to receive this award. I have great respect for previous winners and the transformative science that they have accomplished by using support from the Pioneer Award mechanism. Given the extremely competitive nature of this award, the scientific community thinks we are on to something potentially transformative to treat and study debilitating neurological diseases. It has taken us a long time to convince them of this and our persistence has paid off, but there is still much more work to be done!”
Disney’s revolutionary approach uses cells as reaction vessels and a disease-causing defect as a catalyst to synthesize treatments within the disease-affected cell itself. Because the treatment is synthesized only in disease-affected cells, these novel compounds provide highly specific therapeutics that only act when a disease is present, offering potential treatments in a selective, precise and unprecedented manner.

In a 2014 study, Disney and his colleagues used the technology to successfully counteract myotonic dystrophy type 2, a relatively mild and uncommon form of the progressive muscle weakening disease, caused by a type of RNA defect known as a “tetranucleotide repeat,” in which a series of four nucleotides is repeated more times than normal in an individual’s genetic code.

There are greater than 30 incurable diseases that Disney’s approach will be applied towards, including include amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig disease), fragile X syndrome (the most common cause of autism) and Huntington’s disease.

Scripps Florida Scientist Wins Prestigious Tetrahedron Young Investigator Award

October 13, 2015 – Matthew Disney, a professor on the Florida campus of The Scripps Research Institute (TSRI), has won the prestigious 2016 Tetrahedron Young Investigator Award for Bioorganic and Medicinal Chemistry.

The award, which was created in 2005 by Tetrahedron Publications, is given to just two individuals each year who have exhibited "exceptional creativity and dedication" in the fields of organic synthesis and bioorganic and medicinal chemistry, respectively.

“I’m honored to be recognized by Tetrahedron for our laboratory’s work,” Disney said. “The award serves as a reminder that persistence pays off. I am especially grateful to all of my co-workers who have worked diligently to push our science forward to tackle some difficult problems.”

Disney added that he is especially appreciative of the award because of his admiration for previous winners, who include TSRI’s Chair of the Department of Chemical Physiology Ben Cravatt and the late Professor Carlos Barbas III.

Tetrahedron Award winners each receive an invitation to present a plenary lecture at the annual Tetrahedron Symposium, which will be held next June in Sitges, Spain.

This latest award comes on the heels of the coveted Pioneer Award from the National Institutes of Health (NIH), which Disney received earlier this month. The Pioneer Award, which carries with it a five-year grant of $4.8 million, is intended to enable scientists to develop groundbreaking approaches with a significant impact on broad areas of biomedical science.
Tetrahedron publishes experimental and theoretical research results in the field of organic chemistry and its application to related disciplines, especially bioorganic chemistry. Areas covered by the journal include the many facets of organic synthesis, organic reactions, natural products chemistry, studies of reaction mechanisms and various aspects of spectroscopy.

**New Study Reveals How Specialized Cells Help Each Other Survive During Times of Stress**

November 3, 2015 – A team led by scientists from the Florida campus of The Scripps Research Institute (TSRI) and the University of Pittsburgh has shown for the first time how one set of specialized cells survives under stress by manipulating the behavior of key immune system cells.

The new study, published recently in the journal *Nature Communications*, involved mesenchymal stem cells—which live in bone marrow and can differentiate into several different cell types used in bone and connective tissue—and macrophages—immune cells that usually respond to infectious agents or damaged cells by engulfing and devouring them.

“This is the first time anyone has shown how mesenchymal stem cells provide for their own survival by recruiting and then suppressing normal macrophage activity,” said TSRI Professor Donald G. Phinney, who led the study with University of Pittsburgh Associate Professor Luis A. Ortiz. “This finally puts the crosstalk between these cells into the context of cell survival.”

The team’s experiments showed that, like all other cells, mesenchymal stem cells experience stress due to tissue injury and inflammation. When this stress results in damage to the mitochondria (the power houses of the cell), the mesenchymal stem cells recruit the immune system’s macrophages—but in an unusual way.

By reengineering macrophage action with secreted microRNA, the stem cells protect themselves from being targeted and instead package their damaged mitochondria into small sacs known as vesicles and send them out to be engulfed by the macrophage.

Once macrophages subsume the damaged mitochondria, the macrophages are able to repurpose the mitochondria for their own use, replenishing their own energy supplies. Blocking the exchange of damaged mitochondrial to macrophages causes death of the stem cells. Therefore, the process is mutually beneficial.

“It’s a transient phenomenon, which then allows the macrophages to use the mitochondria for their own survival needs,” Phinney said. “All cells want to survive; that’s what they do.”

In addition to Phinney, the other first author of the study, “Mesenchymal Stem Cells Use Extracellular Vesicles to Outsource Mitophagy and Shuttle Micrornas,” is Michelangelo Di Giuseppe of the University of Pittsburgh. Other authors include Ortiz, Joel Njah, Sruti Shiva, Claudette M. St Croix, Donna B. Stolz, Simon C. Watkins, Y. Peter Di, George D. Leikauf and Jay Kolls of the University of Pittsburgh; Ernest Sala of Hospital Son Espases, Spain; David W.H. Riches of National Jewish Health, Denver, CO; Giuseppe Deiuliis and Naftali Kaminski of
Yale University; Siddaraju V. Boregowda of TSRI; and David H. McKenna of the University of Minnesota. See http://www.nature.com/ncomms/2015/151007/ncomms9472/full/ncomms9472.html

This work was funded by the National Institutes of Health (grants R01HL114795, R01HL110334 and R24 OD018254).

Scripps Florida Scientists Discover New Compounds with Potential to Treat Persistent Tuberculosis

November 17, 2015 – Tuberculosis has been infecting humans for several millennia, making it one of the most horribly successful diseases in history. Today, it is still a major killer, responsible for some 1.5 million deaths each year.

In a substantial number of cases—some two billion, in fact—the tuberculosis bacteria (Mycobacterium tuberculosis) isn’t active at all. Instead, it hides inside cell aggregates, latent and persistent, waiting to break out.

Now, scientists from the Florida campus of The Scripps Research Institute (TSRI) have discovered several first-in-class compounds that target these hidden infections by attacking a critical process the bacteria use to survive in the hostile environment of the lungs. The study, which was published recently online ahead of print by the journal ACS Chemical Biology, was led by Kate Carroll, a TSRI associate professor.

“With the help of Scripps Florida’s high-throughput screening facility, we looked at nearly 40,000 compounds before we uncovered these new, potent inhibitors that attack an enzyme critical to the survival of persistent tuberculosis,” Carroll said. “Thanks to our collaborators in India with access to drug-resistant patient isolates, we were able to demonstrate that these compounds also show excellent activity against multidrug resistant (MDR) and extensively drug-resistant (XDR) strains, in addition to the standard laboratory reference strain, H37Rv, of M. tuberculosis.”

In 2013, the World Health Organization reported that nearly a quarter of all new and previously treated cases of the disease were multidrug resistant—difficult to diagnose and even more difficult to treat.

James Collins, who is the Termeer Professor at the Massachusetts Institute of Technology (MIT) and the Broad Institute of MIT and Harvard University, praised the new study, saying, “This is a marvelous work and an important contribution to the field.”

A Promising New Target

The study identified at least three different structural classes of compounds known as APSR inhibitors active against the bacteria, particularly those multidrug-resistant and extensively drug-resistant strains. The APSR enzyme is essential to the production of reduced sulfur compounds
needed to stabilize the cellular environment—and the target of Carroll’s new inhibitors, which aim to kill persistent tuberculosis by disrupting this balance.

“*M. tuberculosis* infects host macrophages,” Carroll said. “These immune cells produce high levels of reactive oxygen and reactive nitrogen species (RONS), which cause oxidative damage to biomolecules, such as lipids, proteins and DNA. For this reason, *M. tuberculosis* depends heavily upon the production of RONS-neutralizing reduced sulfur compounds, including mycothiol and cysteine. This is why the reductive sulfur assimilation pathway is such a powerful target. Once you reduce the level of reduced sulfur compounds, you eliminate a central mechanism that all bacteria, including *M. tuberculosis*, use to survive host defense systems.”

The new study may encourage exploration of this pathway as a target for development of other antibacterial treatments.

"The first-in-class inhibitors in our study satisfy many criteria expected of a lead scaffold for anti-tuberculosis therapeutics,” said Prakash Palde, the first author of the study and a research associate in the Carroll lab. “But the presence of APSR enzyme in other pathogenic bacteria also means our new inhibitors may have the potential to be developed in to a class of broad-spectrum antibiotics.”

In addition to Carroll and Palde, other authors of the study, “First-In-Class Inhibitors of Sulfur Metabolism with Bactericidal Activity against Non-Replicating *M. tuberculosis,*” include Laura E. Pedró Rosa, Franck Madoux, Peter Chase, Vinayak Gupta, Timothy Spicer and Louis Scampavia of TSRI; and Ashima Bhaskar and Amit Singh of the Indian Institute of Science, Bangalore, India. For more information, see [http://pubs.acs.org/doi/abs/10.1021/acschembio.5b00517](http://pubs.acs.org/doi/abs/10.1021/acschembio.5b00517)

The work was supported by the National Institutes of Health (grant number GM087638), the Ministry of Science and Technology, India (BT/PR5020/MED/29/454/2012), and the Wellcome-DBT India Alliance (500034/Z/09/Z).

**Scripps Florida Scientists Unveil Critical Mechanism of Memory Formation**

November 19, 2015 – In a new study that could have implications for future drug discovery efforts for a number of neurodegenerative diseases, scientists from the Florida campus of The Scripps Research Institute (TSRI) have found that the interaction between a pair of brain proteins has a substantial and previously unrecognized effect on memory formation.

The study, which was published November 19, 2015 by the journal *Cell*, focuses on two receptors previously believed to be unrelated—one for the neurotransmitter dopamine, which is involved in learning and memory, reward-motivated behavior, motor control and other functions, and the other for the hormone ghrelin, which has been connected to appetite as well as the distribution and use of energy.
“Our immediate question was, what is the ghrelin receptor doing in the brain since the natural ligand—ghrelin—for it is missing? What is its functional role?” said Roy Smith, chair of TSRI’s Department of Metabolism and Aging. “We found in animal models that when these two receptors interact, the ghrelin receptor changes the structure of the dopamine receptor and alters its signaling pathway. This is important because many drugs used currently in the clinic, for example for schizophrenia, have poor compliance because of adverse side effects. This discovery opens the door to using neuronal agents that indirectly modify dopamine signaling by pharmacologically targeting the ghrelin receptor—and potentially dramatically reducing side effects.”

“This concept has potentially profound therapeutic implications,” said Andras Kern, the first author of the study and a staff scientist in the Smith lab, “pointing to a possible strategy for selective fine-tuning of dopamine signaling in neurons related to memory. By using small molecules binding to the ghrelin receptor we can enhance or inhibit dopamine signaling.”

Challenging the current theory, which involves canonical dopamine signaling in neurons, the new study shows that the biologically active ghrelin-dopamine receptor complex produces synaptic plasticity, the ability of the brain’s synapses (parts of nerve cells that communicate with other nerve cells) to grow and expand, the biological process underpinning long-term memory formation.

In addition, when the researchers blocked the ghrelin receptor, dopamine-dependent memory formation was inhibited in animal models, demonstrating the mechanism is essential to that process.

Combined with conclusions from earlier studies that showed a significant role for the ghrelin receptor in neurons that regulate food intake, insulin release and immune system deterioration due to aging, the new study further expands the ghrelin receptor’s importance. In animal models, ghrelin inhibits neuronal loss associated with Parkinson's disease, and stroke, Smith noted, and the new study underlines its possible role in treating memory loss, age related or otherwise. “All in all, it’s a pretty amazing receptor,” he said.

In addition to Smith and Kern, other authors of the study, “Hippocampal Dopamine/DRD1 Signaling Dependent on the Ghrelin Receptor,” are Maria Mavrikaki, Celine Ullrich, Rosie Albarran-Zeckler and Alicia Faruzzi Brantley of TSRI.

This work was supported by the National Institutes of Health (grant R01AG019230).

**Scripps Florida Scientists Reveal Potential Treatment for Life-Threatening Viral Infections**

*The Findings Point to New Therapies for Dengue, West Nile and Ebola*
Scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown for the first time how a previously unknown process works to promote infection in a number of dangerous viruses, including dengue, West Nile and Ebola.

The new study also points to a potential treatment, an experimental antibiotic that appears to inhibit infection by these deadly viruses, all of which lack vaccines and treatments.

The study, which was published recently by the journal *Proceedings of the National Academy of Sciences* (*PNAS*), was led by TSRI Associate Professor Hyeryun Choe.

“Most of these viruses use a specific molecule to enter cells,” Choe said. “In the new study, we were able to show how a *second* molecule plays a major and previously unknown role in that process. We also show an antibiotic called duramycin inhibits the actions of this molecule. This looks to be a promising broad-spectrum antiviral strategy and deepens our understanding of the entire infection process.”

**Emerging Health Concern**

The viruses in question belong to several families, including the flavivirus and filovirus families. Flaviviruses like dengue and West Nile viruses cause tens of thousands of deaths each year. Filoviruses like Ebola have emerged as major health concerns, particularly in tropical and subtropical areas such as the recent highly publicized Ebola outbreak in West Africa. Perhaps the greatest concern is dengue virus. More than one third of the world’s population is estimated to be at risk for dengue and more than 100 million people are estimated to be infected annually, according to recent studies.

The viruses take advantage of the process that normally occurs during programmed cell death or apoptosis. During this process, a lipid usually found on the inner side of the cell membranes, specifically phosphatidylserine (PS), shifts to the surface. Apoptosing cells are then recognized by PS receptors on phagocytes—cells that devour invading pathogens and dying cells—and engulfed by them.

When cells are dying from a virus infection, their freshly exposed PS is grabbed by the exiting virus and phagocytes engulf the virus. Once engulfed, the virus quickly turns the cell's own biology on its head, forcing it to produce copies of the virus.

**New Insights**

In the new study, Choe and her colleagues showed how another lipid known as phosphatidylethanolamine (PE), which is present on the viral surface, also contributes to the viral entry process.

“Despite the name, we found that PS receptors also detect PE, and viruses are able to take advantage of the abundance of PE on their surface,” said Audrey Stéphanie Richard, the first author of the study and a research associate in the Choe lab. “Through their PE, they latch onto
the PS receptors on the host cell, taking control of the process and insuring entry and replication.”
Duramycin blocks viral entry into the cells by binding to the virus’s PE, preventing the virus from using it to latch onto the PS receptors on the cell. Duramycin, which is currently used as an imaging agent, binds specifically to PE.

Disrupting the relationship between these two molecules could open the door to new and novel antiviral strategies, potentially including duramycin and similar PE-inhibitors.

“This new study goes a long way in helping us understand how so-called PS receptors contribute to flavivirus and filovirus infections and how we can block them through the PE-binding compounds,” Choe said.

The study also shows that PE is exposed on the surface of apoptotic cells and promotes their uptake by phagocytes.

In addition to Choe and Richard, other authors of the study, “Virion-Associated Phosphatidylethanolamine Promotes TIM1-Mediated Infection by Ebola, Dengue, and West Nile Viruses,” are Adam Zhang, Sun-Jin Park, Michael Farzan and Min Zong of TSRI. See www.pnas.org/content/early/2015/10/30/1508095112.full.pdf?sid=e30bde52-fc0f-4925-94f3-e7316560d5a5

The work was supported by the National Institutes of Health (grant AI110692).

**Scripps Florida Scientists Create 'Fingerprints' for Major Drug Development Targets**

JUPITER, FL – December 2, 2015 – For the first time, scientists from the Florida campus of The Scripps Research Institute (TSRI) have created detailed “fingerprints” of a class of surface receptors that have proven highly useful for drug development.

These detailed “fingerprints” show the surprising complexity of how these receptors activate their binding partners to produce a wide range of signaling actions.

The study, which was published this week in the journal *Science Signaling*, focuses on interactions of G protein-coupled receptors (GPCRs) with their signaling mediators known as G proteins. GPCRs—currently accounting for about 40 percent of all prescription pharmaceuticals on the market—play key roles in many physiological functions because they transmit signals from outside the cell to the interior. When an outside substance binds to a GPCR, it activates a G protein inside the cell to release components and create a specific cellular response.

“Until now, it was generally believed that GPCRs are very selective, activating only a few G proteins they were designed to work with,” said TSRI Associate Professor Kirill Martemyanov, who led the study. “It turns out the reality is much more complex.”

Ikuo Masuho, a senior research associate in the Martemyanov lab, added, “Our imaging technology opens a unique avenue of developing drugs that would precisely control complex
GPCR-G protein coupling, maximizing therapeutic potency by activating G proteins that contribute to therapeutic efficacy while inhibiting other G proteins that cause adverse side effects.”

The study found that individual GPCRs engage multiple G proteins with varying efficacy and rates, much like a dance where the most desirable partner, the GPCR, is surrounded by 14 suitors all vying for attention. The results, as in any dance, depend on which G proteins bind to the receptor—and for how long. The same receptor changes G protein partners—and the signaling outcome—depending on the action of the signal received from outside of the cell.

This finding was made possible by novel imaging technology used by the Martemyanov lab to monitor G protein activation in live cells. Using a pair of light-emitting proteins, one attached to the G protein, the other attached to what’s known as a reporter molecule, Martemyanov and his colleagues were able to measure simultaneously both the signal and activation rates of most G proteins present in the body.

“Our approach looks at 14 different types of G proteins at once—and we only have 16 in our bodies,” he said. “This is as close as it can get to what is actually happening in real time.”

In the accompanying commentary in *Science Signaling*, Alan Smrcka, a professor at University of Rochester Medical School and a prominent GPCR researcher, wrote, “[The findings] suggest the power of the GPCR fingerprinting approach, in that it could predict the G protein coupling specificity of a GPCR in a native system, which was previously undetected by conventional analysis. This could be very helpful for identifying previously unappreciated signaling pathways downstream of individual GPCRs that could be useful therapeutically or identified as potential side effects of GPCRs.”

In addition to Martemyanov and Masuho, other authors of the study, “Distinct Profiles of Functional Discrimination Among G Proteins Determine the Actions of G Protein–Coupled Receptors,” are Olga Ostrovskaya and Keqiang Xie, both of TSRI at the time of the study, and Grant M. Kramer and Christopher D. Jones of Florida Atlantic University. For the study, see http://stke.sciencemag.org/content/8/405/ra123; for the commentary, see http://stke.sciencemag.org/content/8/405/fs20

The work was supported by the National Institutes of Health (grants EY018139, DA026405, and DA036596).

**TSRI Team Finds Unique Anti-Diabetes Compound Using Powerful New Drug-Discovery Method**

JUPITER, FL – December 7, 2015 – Scientists from The Scripps Research Institute (TSRI) have deployed a powerful new drug discovery technique to identify an anti-diabetes compound with a novel mechanism of action.
The finding, which appeared online ahead of print in *Nature Communications*, may lead to a new type of diabetes treatment. Just as importantly, it demonstrates the potential of the new technique, which enables researchers to quickly find drug candidates that activate cellular receptors in desired ways.

“In principle, we can apply this technique to hundreds of other receptors like the one we targeted in this study to find disease treatments that are more potent and have fewer side effects than existing therapies. It has been a very productive cross-campus collaboration, so we’re hoping to build on its success as we continue to collaborate on interrogating potential therapeutic targets,” said Patricia H. McDonald, an assistant professor at TSRI’s Jupiter, Florida campus and a senior investigator of the study.

McDonald’s laboratory collaborated on the study with the laboratory of Richard A. Lerner, the Lita Annenberg Hazen Professor of Immunochemistry at TSRI’s La Jolla campus, and with other TSRI groups. Lerner has pioneered techniques for generating and screening large libraries of antibodies or proteins to find new therapies.

### In Search of a Better Activator

Three years ago, Lerner and colleagues devised a technique called autocrine selection, which enables scientists to screen very large libraries of molecules to find those that not only bind a given cellular receptor but also activate it to bring about a desired therapeutic effect. Since then, the Lerner laboratory and collaborating scientists have used the technique to find new molecules that block cold virus infection, boost red blood cell production and kill cancer cells, among other effects.

For the new study, Lerner and his laboratory used the technique to target a receptor linked to type 2 diabetes, a life-shortening disease estimated to affect 30 million people in the US alone.

The GLP-1 receptor, as it is known, is expressed by insulin-producing “beta cells” in the pancreas. Several drugs that activate this receptor—drugs called GLP-1 receptor agonists—are already approved for treating type 2 diabetes. In this case, the TSRI team’s aim was to find a molecule that activates the GLP-1 receptor in a unique way.

The GLP-1 receptor belongs to a large class of receptors known as G protein-coupled receptors (GPCRs). Scientists recently have come to understand that when a molecule activates a GPCR, it doesn’t necessarily trigger a single chain of biochemical signals within the cell. In fact, most GPCR agonists trigger signals via multiple distinct pathways—one being via a so-called G protein and another via a protein known as beta-arrestin. In some cases, a “biased agonist” that principally activates just one of these pathways would work better than one that activates both. In this case, Lerner and his laboratory teamed up with McDonald, an expert on GPCRs and metabolic disease, to find a molecule that would preferentially activate the GLP-1 receptor’s G protein pathway.

To start, researchers in Lerner’s laboratory, including Hongkai Zhang, a senior staff scientist and co-first author of the study, generated a library of candidate molecules—based on a known GLP-
1 receptor agonist, Exendin-4, a small protein (peptide) originally found in the venom of Gila monster lizards; a synthetic version of this protein is now used as a type 2 diabetes medication. Zhang created about one million new peptides by randomly varying one end of Exendin-4—the end that normally activates the G protein and beta arrestin pathways.

“The idea was that at least one of these many variants would induce a change in the shape of the GLP-1 receptor that would activate the G-protein pathway without activating the beta arrestin pathway,” Zhang said.

Using the autocrine selection system, Zhang and colleagues rapidly screened these variant peptides and eventually isolated one, P5, that potently and selectively activated the GLP-1 receptor’s G-protein pathway. An initial test in healthy mice showed that P5 worked well at boosting glucose tolerance—at about one-hundredth the dose of Exendin-4 needed for the same effect.

Protein expert Philip E. Dawson, an associate professor at TSRI’s La Jolla campus, synthesized sufficient quantities of P5, and McDonald and her laboratory performed more advanced tests in cultured cells and in mice.

A Different Mechanism

Exendin-4 and other GLP-1 receptor agonists work in part by strongly stimulating pancreatic beta cells to produce more insulin—which signals muscle and fat cells to draw glucose from the blood, thus lowering blood glucose levels.

McDonald and her team found that although P5 equals or outperforms Exendin-4 in standard mouse models of diabetes, it stimulates insulin production only weakly.

“We didn’t expect that, but in fact, it was a nice finding because less reliance on stimulating insulin could mean less stress on the beta cells,” said Emmanuel Sturchler, staff scientist in the McDonald laboratory and co-first author of the study.

Investigating further, the team found that while the peptide doesn’t make mice fatter or heavier, it triggers the growth of new fat cells. In typical obesity-related diabetes, fat cells grow larger, not more numerous, and as they grow larger, they lose their ability to respond to insulin (insulin resistance). The proliferation of fat cells with P5 was accompanied by signs of increased insulin sensitivity in those cells, suggesting that the peptide works in part by alleviating insulin resistance.

Exendin-4 induces a feeling of satiety, causing mice (and people) to modestly lower food intake and thus lose weight. But the researchers found that P5 lacks this mechanism and appears to have no effect on appetite or weight.

“P5’s mechanisms of action turned out to be quite different from Exendin-4’s, and we think that this finding could lead to new therapeutics,” Sturchler said.
The team will now look for opportunities to develop P5 into a new diabetes drug. The researchers also see this as the first of many discoveries of GPCR-targeting compounds with unique and potentially valuable properties—as well as discoveries in basic GPCR biology.

In addition to McDonald, Lerner, Zhang, Dawson and Sturchler, other co-authors of the paper, “Autocrine selection of a GLP-1R G-protein-biased agonist with potent antidiabetic effects,” were Jiang Zhu, Ainhoa Nieto, Philip A. Cistrone, Jia Xie, LinLing He, Kyungmoo Yea, Teresa Jones, Rachel Turn, Peter S. Di Stefano and Patrick R. Griffin. For more information, see http://www.nature.com/ncomms/2015/151201/ncomms9918/full/ncomms9918.html

The research was funded in part by the JPB Foundation and Zebra Biologics, Inc.

New Scripps Florida Compound Successfully Targets Hard-to-Treat Breast Cancer

JUPITER, FL – December 16, 2015 – Findings from a new study led by scientists from the Florida campus of The Scripps Research Institute (TSRI) suggest a potent new therapeutic approach for a number of hard-to-treat breast cancers.

The study points to an enzyme called casein kinase 1δ (CK1δ), a critical regulator of growth, as a novel and highly vulnerable therapeutic target. Increased CK1δ expression is common to breast cancer, including the difficult-to-treat subtype called “triple negative breast cancer” (those cancers not driven by estrogen, progesterone, or the HER-2/neu gene), affecting 10 to 20 percent of breast cancer patients.

The study, which was published today in the journal Science Translational Medicine, was a collaboration among the Florida labs of Derek Duckett and William R. Roush, both of TSRI, and John Cleveland, formerly of TSRI and currently at the Moffitt Cancer Center.

“Our findings confirm that aberrant CK1δ regulation promotes tumor growth in breast cancers by activating the protein β-catenin,” said Duckett, an associate professor at Scripps Florida. “The best news, however, is that we have been able to treat CK1δ-expressing breast cancers with a highly selective and potent CK1δ inhibitor developed by Bill Roush’s lab that triggers rapid tumor cell death.”

At the beginning of the study, the team knew that the β-catenin protein was an oncogene in many cancers, but it was unclear why it was activated in these breast cancer types since they lacked typical mutations in those pathways. The researchers suspected the link could be overexpression of CK1δ. Their experiments showed that indeed to be the case.

To confirm the new target, the study used the Roush lab compound, called SR-3029. SR-3029 was remarkably successful at blocking the growth of tumors in both animal models and in studies with tumor tissue from breast cancer patients.
“SR-3029 removes β-catenin from cancer cells, killing the tumors,” explained Duckett. “This is an extraordinarily promising strategy for targeted treatment with SR-3029, especially in breast cancers that lack targeted treatment options.”

“These results are just the tip of the iceberg,” added Roush, who is professor, associate dean and executive director of medicinal chemistry at TSRI. “Inhibitors such as SR-3029 are being studied in a host of different cancers, and we are hopeful this platform can be translated into clinical applications.”

The first author of the study, “Therapeutic Targeting of Casein Kinase 1δ in Breast Cancer,” is Laura H. Rosenberg, a TSRI research associate at the time of the study. In addition to Rosenberg, Duckett, Roush and Cleveland, other authors include Marie Lafitte, Victor Quereda, Wayne Grant, Weimin Chen, Mathieu Bibian, Yoshihiko Noguchi and Mohammad Fallahi of TSRI; Chunying Yang of Moffitt Cancer Center and Research Institute; and Jenny C. Chang of Houston Methodist Hospital.

This work was supported in part by the National Institutes of Health (grants CA175094, U54MH074404, P30-CA076292), Rendina Family Foundation, Shear Family Foundation, ThinkPink Kids Foundation, the State of Florida and Moffitt Cancer Center & Research Institute.

**Scripps Florida Scientist Awarded $2 Million to Study Role of Single Neurons in Memory and Aging**

JUPITER, FL – December 16, 2015 – A scientist from the Florida campus of The Scripps Research Institute (TSRI) has been awarded approximately $2 million from the National Institutes of Health to study the impact of aging and age-related disease on the inner workings of a single type of nerve cell.

Ronald Davis, chair of the Department of Neuroscience at TSRI, is the principal investigator for the five-year grant.

The project uses as its research model *Drosophila melanogaster*, the common fruit fly. The fruit fly is widely used in these types of studies because humans and flies share many of the same mechanisms involved in learning and memory.

The neuron under study, known as the dorsal paired medial neuron (DPM), is unusual in its structure and function. Only one DPM neuron exists per hemisphere in the brain, and earlier studies showed it functions in specific phases of memory. The neuron’s overall function degrades with age, leading to poor intermediate- and long-term memory in older flies.

“The study of this unique neuron offers a special opportunity to relate the biology of a single type of neuron to aging and memory impairment due to age,” Davis said. “While our goal is to expand the understanding of the mechanisms of normal aging and of age-related diseases, this knowledge could significantly advance the development of novel therapeutics.”
The new study will focus on the synaptic connections—the junction between two nerve cells that enable them to communicate with one another—in young and aged flies, as well as how gene expression within this neuron type changes with age.

The number of the grant is 1R01AG049037.

**Remicade® Developer Funds New Super-Resolution Microscope at Scripps Florida**

JUPITER, FL – January 29, 2016 – The co-developer of Remicade®, one of the three top-selling drugs in the world, has donated more than $500,000 to fund what will be known as the Iris and Junming Le Foundation Super-Resolution Microscopy Facility on the Florida campus of The Scripps Research Institute (TSRI).

“We are grateful to Junming and Iris for their generous contribution,” said Chair of the TSRI Department of Neuroscience Ronald Davis, who will oversee the new facility. “The gift will have a dramatic and highly positive effect on the brain science pursued by our department. This is the perfect opening to what will be a genuinely state-of-the-art facility right here in Jupiter.”

The new donation will support the purchase of a powerful microscope that will give Scripps Florida neuroscientists an extraordinarily detailed view of the brain.

“Our foundation gives money to the best institutions and hospitals to support basic medical research and patient care through those projects we think will be successful,” said Junming Le, chairman and director of The Iris and Junming Le Foundation and adjunct associate professor of microbiology at New York University School of Medicine. “This is certainly one of them. When I learned that this microscope could advance the understanding of the brain and its function, I realized this would be an important investment for us. That kind of information could lead to breakthroughs in diseases like Alzheimer’s.”

The new microscope will be one of the most advanced available. Known as a structured illumination microscope, the technology uses a super-imposed pattern (grate), taking multiple images at various angles. These images are then merged—effectively doubling the resolution of a traditional light microscope.

“With this super-resolution microscopy,” Davis said, “we will be able to see synapses between neurons and to actually count them—to determine, for example, if the number of neurons in a brain affected by Alzheimer’s or Parkinson’s disease is different than a normal brain. This is a nearly unimaginable leap forward.”

Funding for The Iris and Junming Le Foundation, based in New York and Boca Raton, is the legacy of Junming Le’s invention of Remicade®, a drug used to treat autoimmune diseases, such as rheumatoid arthritis, psoriasis, Crohn’s disease and ulcerative colitis. Remicade®, which is currently manufactured and marketed by Johnson & Johnson and Merck, has been prescribed to more than two million people worldwide.
Scripps Florida Scientists Win $1.2 Million to Study New Strategies for Treating Obesity, Diabetes, Cardiovascular Disease and Muscle Decline

JUPITER, FL – February 3, 2016 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have been awarded nearly $1.2 million from the National Institutes of Health (NIH) to create a series of drug candidates that advance more effective treatments for a range of conditions, including obesity, type-2 diabetes, cardiovascular disease and muscle atrophy.

The three-year project will be led by Scripps Florida’s Associate Professor Theodore M. Kamenecka and Professor Patrick R. Griffin.

The team will focus on drug candidates that affect a family of medically important molecules known as nuclear receptors, which regulate gene expression in response to signals from various binding partners, including estrogen, progesterone, thyroid hormone and retinoic acid (vitamin A). First discovered in the 1960s, 48 nuclear receptors have been identified in humans.

However, a number of these receptors, called orphan receptors, have no known activator molecule or the identity of the activating molecule is controversial. Among these orphan receptors are estrogen-related receptors ERRα, ERRβ and ERRγ. These are the topic of the new research.

“While we’re looking at all three protein receptors,” Kamenecka said, “we want to focus on ERRγ because it’s closely associated with tissues such as heart, kidney, brain and skeletal muscles. Our goal is to optimize our current series of synthetic ERRγ activators for potency and selectivity to advance our ongoing study of the receptor’s role in various diseases.”

Previous research has shown that animal models genetically engineered to lack ERRγ exhibited decreased capacity for exercise and mitochondrial function in muscles compared to normal. In contrast, models with increased expression of ERRγ showed greater oxygen consumption, treadmill endurance and mitochondrial function and were resistant to diet-induced weight gain.

“Using the unique resources at Scripps Florida and the integration of chemistry and biology, we are confident we will develop selective activators (often referred to as modulators, as these molecules alter the gene program that nuclear receptors modulate). If we are successful, several Scripps Florida colleagues have expressed interest in using our ERRγ modulators to study muscle function and exercise capacity in the context of aging,” Griffin added. “We’re looking at a wide range of compounds to modulate this receptor’s activity in beneficial ways.”

The number of the grant, awarded by the NIH’s Eunice Kennedy Shriver National Institute of Child Health and Human Development, is 1R01HD087046.
Local Neuroscientists Gather for Synapse 2016

Local Universities and Research Institutions Collaborate for the Popular Neuroscience Networking Event

JUPITER, FL – February 5, 2016 – More than 200 of the brightest scientific minds in the region gathered today at the Florida campus of The Scripps Research Institute (TSRI) to network and share their research findings. In collaboration with the Palm Beach Chapter of the Society for Neuroscience, Florida Atlantic University (FAU) and Max Planck Florida Institute (MPFI), Scripps Florida hosted “Synapse 2016,” an annual neuroscience networking event for students and research scientists.

“We couldn’t be more pleased or more excited to host Synapse 2016 at Scripps Florida,” said Ron L. Davis, Ph.D., TSRI’s Department of Neuroscience founding chair. “This is an opportunity for scientists from our campus, Max Planck, FAU and other local institutions to share their research, their ideas and their enthusiasm about the work they’re doing. For those of us who have chosen Palm Beach County to live and work, this is exactly what we hoped would happen—a growing spirit of collaboration that is rapidly becoming the hallmark of the Jupiter scientific community. It’s a great opportunity for everyone in the neuroscience field.”

Representatives from nearby Nova Southeastern University, Torrey Pines Institute and Palm Beach State College also took advantage of the opportunity. More than 30 posters were displayed, covering an impressive range of projects on topics such as behavioral studies, neural computations and molecular neuroscience.

“Collaborative events like Synapse are an example of what makes this Jupiter campus so exciting and valuable for our students and scientists,” said Scientific Director and CEO at MPFI David Fitzpatrick, Ph.D. “It’s the perfect opportunity and setting to learn more about the research being done here in Palm Beach County and to explore opportunities to work together.”

The event’s coordinators encouraged interaction by strategically placing scientists of different specialty areas and their posters next to each other to spark conversations. Additionally, the open submission process was designed to allow scientists and students of all levels to have an equal opportunity to present their work.

“All three institutions in the Jupiter community are leading key initiatives from their neuroscience programs,” said Rod Murphey, Ph.D., Jupiter Life Science Initiative director and FAU’s Department of Biological Sciences chair. “It’s an exceptional opportunity for scientists to collaborate and present different ideas on their areas of research.”

Scripps Florida Researchers Develop 'LIGHTSABR'—A Cheap, Portable Drug-Discovery System

JUPITER, FL – February 10, 2016 – Screening large “libraries” of compounds to find those with a desired biological activity is a powerful method for discovering new drugs, but requires a large, expensive and dedicated facility. Now, scientists at the Florida campus of The Scripps Research
Institute (TSRI) have devised the central component of a screening system that would be orders of magnitude smaller and cheaper.

“We’ve developed a device that can do the functional equivalent of high-throughput compound screening on an ultra-miniaturized scale,” said the study’s principal investigator Brian M. Paegel, an associate professor at TSRI.

The advance, published recently online ahead of print in Analytical Chemistry, follows a previous study from the Paegel laboratory in ACS Combinatorial Science that described the synthesis of miniaturized DNA-encoded compound libraries. The new screening device is designed to work with the new type of library.

**One-Bead, One-Compound**

Current high-throughput screening systems typically occupy 10,000 square feet of space or more and cost millions of dollars. They rely heavily on robotic devices that retrieve compounds from the library, place each compound into a separate small well in an “assay microplate” and measure each compound’s biological activity—for example, whether the compound inhibits a particular enzyme involved in viral replication.

Being almost entirely automated and relatively quick, such systems can rapidly screen the tens or hundreds of thousands of compounds in a typical library. But the great cost of these high-throughput screening systems limits their use to locations at pharmaceutical companies and large research institutions. The Scripps Florida campus houses one of the most active high-throughput screening facilities outside the pharmaceutical industry.

The new approach starts with the use of “one-bead-one-compound” (OBOC) libraries, in which individual compounds are chemically attached to microscopic beads. Over the past two decades, many laboratories have begun to work with OBOC libraries of one type or another, which are so quickly and cheaply prepared and are so compact that such libraries are essentially laboratory consumables. “It is possible to generate an OBOC library of millions of compounds in a week for about $500,” said Alexander K. Price, a senior research associate in the Paegel laboratory and lead author of the new study.

**LIGHTSABR**

There are considerable technical challenges involved in putting bead-borne compounds through miniature screening devices. But, as they report in their new paper, Paegel and Price were able to engineer a benchtop-scale device that meets these challenges and can screen OBOC libraries.

The device is built on the microfluidics principles that also underlie inkjet printer technology. Using a “suspension hopper,” which Paegel and Price described in a 2014 Analytical Chemistry paper, the device introduces OBOC library beads into tiny liquid droplets that contain the assay of interest, such as an enzymatic activity assay. The volume of these assay droplets is about 100,000 times less than the volumes used for high-throughput screening assays.
The device then frees each compound from its bead with a photochemical reaction induced by ultraviolet (UV) light and, after an appropriate period of incubation, records the result in each droplet.

Dubbed LIGHTSABR (Light-Induced and Graduated High-Throughput Screening After Bead Release) for its light-based cleavage of compounds from their carrier beads, the device overcomes significant technical hurdles concerning the smooth flow of droplets, the absorption of stray UV irradiation and calibration of the UV waveguide.

A key innovation is that the technique allows users to vary the UV illumination to adjust the amount of a compound cleaved from its bead—and thus adjust the dose of the compound being tested. The team successfully demonstrated this dosing function using an assay designed to find inhibitors of HIV-1 protease, a key enzyme involved in the replication of the virus that causes AIDS.

The next step for Paegel and Price is to apply the microfluidic LIGHTSABR and the laboratory’s DNA-encoded OBOC libraries. “In addition to antiviral compounds, we are also pursuing new antibiotics and other drug classes that address the emergence of resistance in rapidly evolving pathogens,” said Paegel.

“Hundreds of laboratories around the world could operate their own miniaturized screening facilities, using their own assays to go after targets that are of most interest to them,” said Price. In addition to Paegel and Price, the study, “hvSABR: Photochemical Dose-Response Bead Screening in Droplets,” was authored by Andrew B. MacConnell of TSRI.

Funding for the research was provided by a Director’s New Innovator Award from the National Institutes of Health (OD008535) and the Defense Advanced Research Projects Agency (N66001-14-2-4057). To view the paper, see http://pubs.acs.org/doi/abs/10.1021/acs.analchem.5b04811

**Scripps Florida Scientists Identify a Memory Suppressor that May Play a Role in Autism**

JUPITER, FL – February 11, 2016 – Discovered only in the 1990s, microRNAs are short molecules that work within virtually all cells. Typically, each one functions as a “dimmer switch” for the expression of one or more genes, regulating a wide variety of cellular processes, including learning and memory.

In a new study published in the February 11, 2016 issue of the journal *Cell Reports*, scientists from the Florida campus of The Scripps Research Institute (TSRI), working in collaboration with scientists from the University of California, Irvine, show that one specific microRNA has strong links to a number of neuropsychiatric disorders, including autism spectrum disorder.

The microRNA, known miR-980, serves as a memory suppressor in multiple brain regions of *Drosophila*, the common fruit fly, a widely recognized substitute for human memory studies.
“We wanted to know what happens to behavior when we change the levels of these microRNAs,” said Ron Davis, chair of TSRI’s Department of Neuroscience. “When we reduced the level of miR-980, the flies had better memory—that’s something new and surprising.”

Davis noted that this specific microRNA regulates neuronal excitability—the nerve’s capacity for firing—and inhibiting it increased both memory acquisition and stability.

Next, Davis and his colleagues tried to uncover which genes miR-980 regulates, identifying 95 specific targets that might fit that bill. Intriguingly, they found that miR-980 targets and inhibits a gene known as A2bp1. This gene previously had been shown to be involved in susceptibility to autism. In addition, it works to promote memory.

“A2bp1 has been shown to be associated with autism spectrum disorder in humans,” said Research Associate Germain Busto, co-first author of the study with Research Associate Tugba Guven-Ozkan. “We discovered that when A2bp1 was overexpressed, it improved memory and that miR-980 also affected memory when artificially modulated. This offers a powerful model describing the gene network potentially underlying autism spectrum disorder.”

“Linking this microRNA to a disease-linked gene may help us to uncover even more nervous system dysfunctions,” added Guven-Ozkan.

Davis speculated that the different neuronal networks that form due to varying levels of A2bp1 may account for the range of intellectual abilities observed in autism spectrum disorder in the fly model.

“But the fact that A2bp1 plays an influential role in autism and epilepsy in people brings a real human connection to the study,” Davis said. “It’s very exciting.”

In addition to Davis, Busto and Guven-Ozkan, other authors of the study, “MiR-980 is a Memory Suppressor MicroRNA that Regulates the Autism-Susceptibility Gene A2bp1,” are Isaac Cervantes-Sandoval of TSRI and Soleil S. Schutte and Diane K. O’Dowd of the University of California, Irvine.

The work was supported by the National Institutes of Health (grant number R37 NS19904, R01 NS052351 and RO1 NS0830009).

**Scripps Florida Scientists Win $1.7 Million Grant to Advance New Strategies to Treat Huntington’s Disease**

JUPITER, FL – February 12, 2016 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have won nearly $1.7 million from the National Institutes of Health’s (NIH) National Institute of Neurological Disorders and Stroke (NINDS) to investigate the mechanisms that contribute to Huntington’s disease, a fatal inherited disease that some have described as having ALS, Parkinson’s and Alzheimer’s—at the same time.
The principal investigator of the new four-year study is TSRI Assistant Professor Srinivasa Subramaniam.

Huntington’s disease is a frightening puzzle, a genetic disorder that attacks a small part of the brain that controls movement, destroying nerves with a barrage of toxicity, yet leaving other parts relatively unscathed. Currently, there is no cure.

The disease is the result of a mistake in the huntingtin gene, some part of it repeated many more times than normal in the genome, leaving it unstable and unable to produce a normal mHtt protein.

“In Huntington’s disease, even though mHtt is expressed throughout the brain and peripheral tissue, it causes neuronal loss and damage in a part of the brain known as the striatum, a process that is not well understood,” Subramaniam said. “If we’re going to develop new ways to prevent or delay the onset of the disease, we have to clearly define the mechanisms that contribute to the death of these neurons. This new grant will help us do that.”

Subramaniam has been something of a pioneer in the study of Huntington’s disease. Previously, he and his colleagues established that an activating protein, called “Rhes,” plays a pivotal role in focusing the toxicity of Huntington’s disease in the striatum.

The new four-year study will focus on the effect of the Rhes signaling pathway on mitochondria, the organelle that provides energy to cells. Any breakdown in the mitochondria can bring on a host of disabilities.

Subramaniam believes the Rhes pathway could offer a target for treating Huntington’s disease. “Drugs that disrupt Rhes could alleviate Huntington’s pathology and motor symptoms,” he said. “Clarifying the mechanisms of this signaling pathway will help us evaluate potential drug candidates for the prevention and treatment of this terrible disease.”

In addition, Subramaniam’s laboratory received two Research Supplements to Promote Diversity awards from NINDS totaling just over $112,000. The grants are designed to improve the diversity of the research workforce by recruiting and supporting students, postdoctoral fellows and eligible investigators from groups underrepresented in health-related research.

The number of the research grant is 1R01NS094577. The numbers of the supplemental grants are 3R01NS087019-01A1S1 and 3R01NS087019-01A1S2.

**Scripps Florida’s Courtney Miller Wins Presidential Early Career Award**

JUPITER, FL – February 18, 2016 – Courtney Miller, associate professor on the Florida campus of The Scripps Research Institute (TSRI), has been selected to receive a Presidential Early Career Award for Scientists and Engineers, the highest honor bestowed by the United States government on young professionals at the outset of their independent research careers.
“These early-career scientists are leading the way in our efforts to confront and understand challenges from climate change to our health and wellness,” President Barak Obama said in a statement. “We congratulate these accomplished individuals and encourage them to continue to serve as an example of the incredible promise and ingenuity of the American people.”

In a process involving 12 federal agencies and coordinated by the Office of Science and Technology Policy within the Executive Office of the President, the award winners are selected annually based on two criteria: innovative research at the frontiers of science and technology, and commitment to community service as demonstrated through scientific leadership, education or community outreach.

The focus of Miller’s lab at Scripps Florida is developing therapeutics for memory disorders, including addiction, post-traumatic stress disorder and Alzheimer’s disease, with a focus on synaptic and neuroepigenetic contributors.

She began studying the role of memory and addiction as a graduate student at the University of California, Irvine. In 2005, she moved to the University of Alabama, Birmingham, for postdoctoral work in the then-nascent field of neuroepigenetics, studying the contribution of DNA methylation to memory. There, she made the fundamental discovery that DNA methylation can serve as a rapid and dynamic regulator of memory formation and storage in the brain. She moved to Scripps Florida in 2009.

Miller, who is an associate editor of the Elsevier journal Neuroepigenetics and 2015 Scripps Outstanding Mentor of the Year, has a passion for advancing women in science and is co-founder of the Professional Women’s Nexus, a 400+ member group with a mission to improve the advancement rate of women in academia and industry.

As a Presidential Early Career Award honoree, Miller will receive up to a five-year research grant to further her scientific investigations. The winners will receive their awards at a Washington, DC ceremony this spring.

Previous recipients of the Presidential Early Career Award include TSRI Professors Erica Ollmann Saphire and Marisa Roberto.

**Scripps Florida Scientists Awarded $2.25 Million to Study Key Mechanisms Behind Some Cancers**

JUPITER, FL – February 24, 2016 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have been awarded a pair of grants totaling more than $2.25 million to study the assembly mechanisms that lie at the root of various cancers.

The grants come from the National Institute of General Medical Sciences of the National Institutes of Health (NIH) and the Department of Defense (DoD).
Katrin Karbstein, a TSRI associate professor, is the principal investigator of the four-year NIH study, which will be carried out in collaboration with the lab of structural biologist Elizabeth Stroupe at Florida State University. The two-year Department of Defense study will be led by Karbstein and John Cleveland of the H. Lee Moffitt Cancer Center and Research Institute.

Karbstein’s research focuses on the assembly of ribosomes—large macromolecular machines required for cell growth that translate RNA into proteins. Defects in the assembly process can lead to serious problems, including cancer.

The NIH-funded study takes a broad look at the ribosome assembly process to unravel the mechanisms by which defects in ribosome maturation can lead to tumors.

“Defects in assembly of the mRNA binding channel, for example, can lead to birth defects, including Diamond Blackfan Anemia—which has been associated with a 30- to 40-fold increased incidence of colon cancer, osteosarcoma and leukemia,” Karbstein said.

For the new DoD-funded study, the team is working to uncover new ways to disrupt the regulatory circuit that promotes aggressively prolific forms of breast cancer. The research will explore the potential of a drug candidate developed in the laboratory of William Roush, a TSRI professor, associate dean of graduate studies and executive director of medicinal chemistry.

This project will focus on the molecule casein kinase 1d (CK1d), which is essential for human ribosome assembly and has been shown to be an important therapeutic target.

“We think this research could accelerate the development of new drugs directed against triple negative breast cancer by expanding our understanding of the action of these new CK1d inhibitors,” Karbstein said.

The number of the NIH grant is 1R01GM117093; the DoD grant, W81XWH-16-1-0009.

**Scripps Florida Scientists Find Way to Predict Activity of Stem Cells**

*Method Could Help Evaluate Potential Stem Cell Therapies for Different Diseases*

JUPITER, FL – February 29, 2016 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have for the first time developed a way to predict how a specific type of stem cell will act against different diseases. With more than 500 stem cell-based therapies currently in clinical trials, the findings could have an impact on evaluating these therapies and developing new ones.

The new study, published recently by the journal *EBioMedicine*, was led by Professor Donald G. Phinney, acting chair of Scripps Florida’s Department of Molecular Therapeutics.

In some respects, stem cells are like coins—they have two sides. One side is their shape-shifting ability to differentiate into other types of cells; the flip side is their function, the effect they have
on health and disease that underscores their therapeutic potential. For many years, Phinney noted, stem cell experts have believed that these two sides were separate and unrelated. The new results, however, challenge that view.

“We found a coordinated link between stem cell properties and their functions,” Phinney said. “With this new information, we can begin to predict how these functions can be manipulated to make the cells more therapeutically relevant.”

Using a type of stem cell known as mesenchymal stem cells (which are derived from bone marrow and give rise to connective tissues, such as bone, cartilage and adipose tissue), Phinney and his colleagues examined levels of a molecule known as TWIST1 in different human donor populations. They found higher levels of TWIST1 produced more angiogenic effects—boosting new blood vessel growth—while lower levels produced more anti-inflammatory and immuno-suppressive effects.

Moreover, team members were able to show that manipulating levels of TWIST1 in both cells and animal models resulted in a predictable change in stem cells’ functional attributes.

Based on their findings, the scientists developed a Clinical Indications Prediction or CLIP scale, which predicts the therapeutic potential of mesenchymal stem cells for a given disease indication based on their levels of TWIST1.

"There are a number of clinical trials testing mesenchymal stem cells to treat arthritis,” said Siddaraju V. Boregowda, the first author of the study and a member of the Phinney lab. “Since angiogenesis is a key part of the disease process, stem cells with high levels of TWIST1 (indicating they are more angiogenic) would not be beneficial. These cells might be helpful instead for indications such as peripheral vascular disease where new vascularization is beneficial. The proposed CLIP scale accurately predicts these indications and contra-indications."

In addition to Phinney and Boregowda, other authors of the study, “A Clinical Indications Prediction Scale Based on TWIST1 for Human Mesenchymal Stem Cells,” are Veena Krishnappa, Christopher L Haga of TSRI and Luis A. Ortiz of the University of Pittsburgh. See http://www.sciencedirect.com/science/article/pii/S2352396415302486

The work was supported by the National Institutes of Health (R24 OD018254, R01 HL110344 and R01 HL114795) and by TSRI.

**CELLebrate2016 at the Gardens Mall to Spotlight Scripps Florida Science**

JUPITER, FL – March 1, 2016 – Cutting-edge science, a host of exciting interactive displays, plus dozens of Scripps Florida scientists will be on hand at the Gardens Mall on Saturday, March 5, 2016, from 10:00 a.m. to 3:00 p.m. for the seventh annual CELLebrate Scripps Florida Science Day.
This celebration of science, located throughout the Garden Mall's lower level, is a free community science festival that features intriguing science demonstrations and fun, interactive exhibits designed to spark the curiosity and imaginations of children and adults alike.

CELebrate2016 promises a day filled with intriguing scientific exhibits and displays, a hands-on approach to science that has been enchanting Palm Beach County families since the Gardens Mall event was first introduced in 2010.

CELebrate2016 will highlight the exciting biomedical research by Scripps Florida scientists with displays that feature work from the institute’s research departments including Cancer Biology, Metabolism & Aging, Neuroscience, Infectious Diseases, Chemistry and Molecular Therapeutics. In addition, the robotic technology group will have its own booth and will feature a robotic arm display.

The chemistry exhibit, always a favorite, will feature everything from exploding hydrogen bubbles to the extreme cold effects of liquid nitrogen. Robotics will feature displays about Scripps Florida’s drug screening capabilities—how specialized robots help scientists search for new therapeutic compounds—and miniature plastic robots “printed” in 3D.

Since its founding in 2004, Scripps Florida has established deep roots in Palm Beach County, while pursuing its mission as a nonprofit organization to advance human health and train the next generation of scientists.

CELebrate2016 offers a chance for the public to meet the scientists behind the research and learn about some of the amazing scientific breakthroughs taking place right here in Palm Beach County.

For more information, see http://www.scripps.edu/florida/education/community/CELebrate.html

Scripps Florida Scientists Win $2.4 Million to Develop New Strategies to Fight Obesity

JUPITER, FL – March 8, 2016 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have been awarded $2.4 million from the National Institutes of Health (NIH) to identify the brain circuits involved in weight control and to develop novel strategies to fight obsessive eating and obesity.

Baoji Xu, a TSRI professor, is the principal investigator of the new four-year study.

“Our long-term goal is to understand the mechanisms that govern control of energy balance in our bodies,” Xu said. “When we finally understand the processes that regulate that balance, we can exploit those findings to develop novel interventions for obesity.”
Despite the enormous cost, there is currently no effective and safe treatment available for obesity, which raises the risk of everything from stroke to diabetes and cancer. Research published last year in *JAMA Internal Medicine* found that more than two-thirds of Americans are either overweight or obese, a major increase over the last 20 years.

For the new study, Xu and his colleagues will focus on a specific protein and its receptor that play a not-well-understood role in regulating the body’s energy balance. This protein is known as brain-derived neurotrophic factor (BDNF), and its receptor is TrkB.

“Although great progress has been made in understanding other energy-regulation molecules, no one realized the importance of the BDNF-TrkB pathway in controlling body weight until about 10 years ago,” Xu said. “Much less is known about this mechanism than many others.”

Xu’s own research has played a key role in demonstrating a clear role for BDNF in controlling body weight. Some preliminary studies in his laboratory found that the deletion of the *TrkB* gene in various sections of the brain in animal models resulted in moderate to severe obesity plus an abnormal rise in appetite and reduced physical activity.

“Since we moved to Scripps Florida, we have greatly increased our effort in dissecting the mechanism by which BDNF regulates appetite and body weight,” Xu said. “We’ve gotten some very good results in identifying the neural circuits that carry out the activities of BDNF in suppressing appetite and stimulating energy expenditure. This new award will allow our laboratory to continue this effort.”

For advancing this research, Xu and his colleagues will employ viral vectors to selectively ablate gene expression in neural circuits and designer receptors exclusively activated by designer drugs (DREADD) to selectively activate or inhibit neurons.

The number of the grant, which was awarded by the NIH’s National Institute of Diabetes and Digestive and Kidney Diseases, is 1R01DK105954.

**Scripps Florida Study Lays Groundwork for Potential Bipolar Disorder Therapies**

JUPITER, FL – March 9, 2016 – Bipolar disorder, which affects nearly eight million Americans, takes a toll not only on patients, but also on their families and communities.

A new study by scientists from the Florida campus of The Scripps Research Institute (TSRI) has identified specific genetic variations closely associated with increased susceptibility to bipolar disorder and other conditions. The discovery may provide a target for new therapies.

In the new study, the researchers focused on a gene known as PDE10A, one of the many genes that has been linked to bipolar disorder, and the proteins this gene produces. These proteins help regulate intracellular levels of a messenger molecule called cAMP (cyclic adenosine...
monophosphate), which is involved in a variety of biological processes including learning and memory.

“We began with the idea that behavioral changes in bipolar subjects might be due to these genetic variations in the cAMP messenger pathway,” said Ron Davis, chair of TSRI’s Department of Neuroscience. “We did find that this was the case and, indeed, that these variations were in one specific gene for the cAMP messenger pathway called PDE10A. The variations that we found in the gene may alter the function of one form of PDE10A and lead to susceptibility to bipolar disorder.”

The research, published recently by the journal *Translational Psychiatry*, examined human brain tissue from patients with bipolar disorder, as well as brain tissue from individuals without the psychiatric disorder.

“The PDE10A19 protein is interesting because we previously didn't know it even existed in the human brain and because it’s found only in other primates—not mice or rats,” said Research Assistant Courtney MacMullen, the first author of the study. “Once we understand how this protein helps neurons remain healthy, we might be able to develop medications to treat neurons when they function abnormally, such as in patients with bipolar disorder and schizophrenia.”

The results suggested abnormal variations in PDE10A19 might alter cAMP signaling by interacting with another protein known as PDE10A2, restricting its activity and disrupting the entire process.

Davis said that the complexity of gene expression in the human brain is greatly underestimated, and that future neurogenetic studies ought to begin with a deep study of each gene’s ability to code for proteins to avoid false conclusions, particularly when it comes to the development of potential therapies.

“We need to know much more about this large family of enzymes and the roles they play in disorders like bipolar disorder,” he said.

In addition to Davis and MacMullen, other authors of the study, “*Novel, Primate-specific PDE10A Isoform Highlights Gene Expression Complexity in Human Striatum with Implications on the Molecular Pathology of Bipolar Disorder*,” are Kyle Vick, Rodrigo Pacifico and Mohammad Fallahi-Sichani of TSRI.

This work was supported by the funding from the State of Florida.

**Scripps Florida Scientists Win $1.4 Million Grant to Develop New Ways to Block Breast Cancer**

JUPITER, FL – March 18, 2016 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have received a $1.4 million grant from the Department of Defense to develop a
series of drug candidates that act against molecules closely linked with the growth of cancer cells.

Donald G. Phinney, a TSRI professor and acting chairman of the Department of Molecular Therapeutics, is the principal investigator of the new three-year grant.

“The focus of our research will be on breast cancer,” Phinney said. “We’re targeting a specific microRNA—microRNAs don’t produce proteins but can still regulate gene expression—because of its pivotal role in breast cancer. By blocking it, we think we can stop or, at the very least, impede tumor growth, with less toxicity than is often associated with chemotherapy.”

Recent research has shown that virtually all cancer cells experience what is known as “hypoxic stress”—periods of low oxygen. But cancer cells can adapt by slowing their growth rate and metabolism, which increases the cells’ ability to survive. Adaptation to hypoxia is now seen as critical to tumor growth, metastasis and development of drug resistance.

The microRNA that is the focus of the new study is induced by low oxygen and plays a vital role in breast cancer cells’ adaptation to that stressful environment.

“The number of the new grant is W81XWH-16-1-0029.
Bohn, who has been a pioneer in the development of pain therapies, will continue to focus on the kappa opioid receptor, which helps regulate the release of dopamine—a neurotransmitter that plays a key role in drug addiction. Drugs of abuse often cause the brain to release large amounts of dopamine, flooding the brain’s reward system and reinforcing the addictive cycle.

“Chronic drug abuse, addiction and depression lead to changes in dopamine-related structures in the brain,” Bohn said. “The kappa opioid receptor may offer a way to fine-tune dopamine signaling in patients who suffer from addiction or depression. This grant will help us develop new chemical means to regulate this receptor and create new drugs for the treatment of addiction and mood disorders.”

The kappa opioid receptor reacts to signals that originate independently from multiple biological pathways, so many drugs targeting it produce unwanted side effects such as sedation. The new research looks for potent new compounds that minimize such side effects.

Bohn said she hopes to advance these compounds to clinical development over the next several years.

The number of the grant is 2R01DA031927.

**Scripps Florida Study Identifies Memory Suppressor Gene That Could Hold Key to New Alzheimer’s Disease Treatments**

JUPITER, FL – April 14, 2016 – While research has identified hundreds of genes required for normal memory formation, genes that suppress memory are of special interest because they offer insights into how the brain prioritizes and manages all of the information, including memories, that it takes in every day. These genes also provide clues for how scientists might develop new treatments for cognitive disorders such as Alzheimer’s disease.

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have identified a unique memory suppressor gene in the brain cells of *Drosophila*, the common fruit fly, a widely recognized substitute for human memory studies.

The study, which was led by Ron Davis, chair of TSRI’s Department of Neuroscience, was published April 14, 2016, in the journal *Neuron*.

Davis and his colleagues screened approximately 3,500 *Drosophila* genes and identified several dozen new memory suppressor genes that the brain has to help filter information and store only important parts. One of these suppressor genes, in particular, caught their attention.

“When we knocked out this gene, the flies had a better memory—a nearly two-fold better memory,” said Davis. “The fact that this gene is active in the same pathway as several cognitive enhancers currently used for the treatment of Alzheimer’s disease suggests it could be a potential new therapeutic target.”
When the scientists disabled this gene, known as DmSLC22A, flies’ memory of smells (the most widely studied form of memory in this model) was enhanced—while overexpression of the gene inhibited that same memory function.

“Memory processes and the genes that make the brain proteins required for memory are evolutionarily conserved between mammals and fruit flies,” said Research Associate Ze Liu, co-first author of the study. “The majority of human cognitive disease-causing genes have the same functional genetic counterparts in flies.”

The gene in question belongs to a family of “plasma membrane transporters,” which produce proteins that move molecules, large and small, across cell walls. In the case of DmSLC22A, the new study indicates that the gene makes a protein involved in moving neurotransmitter molecules from the synaptic space between neurons back into the neurons. When DmSLC22A functions normally, the protein removes the neurotransmitter acetylcholine from the synapse, helping to terminate the synaptic signal. When the protein is missing, more acetylcholine persists in the synapse, making the synaptic signal stronger and more persistent, leading to enhanced memory.

“DmSLC22A serves as a bottleneck in memory formation,” said Research Associate Yunchao Gai, the study’s other co-first author. “Considering the fact that plasma transporters are ideal pharmacological targets, drugs that inhibit this protein may provide a practical way to enhance memory in individuals with memory disorders.”

The next step, Davis added, is to develop a screen for inhibitors of this pathway that, independently or in concert with other treatments, may offer a more effective way to deal with the problems of memory loss due to Alzheimer’s and other neurodegenerative diseases.

“One of the major reasons for working with the fly initially is to identify brain proteins that may be suitable targets for the development of cognitive enhancers in humans,” said Davis. “Otherwise, we would be guessing in the dark as to which of the more than 23,000 human proteins might be appropriate targets.”

In addition to Davis, Gai and Liu, Isaac Cervantes-Sandoval of TSRI was an author of the study, “Drosophila SLC22A Transporter is a Memory Suppressor Gene that Influences Cholinergic Neurotransmission to the Mushroom Bodies.”

The work was supported by grants from the National Institutes of Health (grants 2R37NS19904 and 2R01NS05235).

**TSRI, Harvard, Stanford and Brandeis Collaborate to Study MicroRNA’s Role in Memory, Sleep and Synapse Function**

JUPITER, FL – April 27, 2016 – A group including scientists from the Florida campus of The Scripps Research Institute (TSRI) has been awarded a grant from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health to study the role of
microRNAs in a range of physiological activities, including memory, sleep, synapse function and movement.

Ron Davis, chair of TSRI’s Department of Neuroscience, will be a principal investigator of the new five-year study with David Van Vactor of Harvard University, Leslie Griffith of Brandeis University and Dennis Wall of Stanford University.

“This new collaboration with some of the best scientists at some of the best universities in the world has the potential to bring us a wealth of new and potentially groundbreaking knowledge about microRNAs,” Davis said. “Because microRNAs are so critical for normal development and physiology, they are a potentially rich source of therapeutic targets. Our new collaboration will help us exploit that potential.”

Scripps Florida will receive approximately $2 million for the project over the next five years. MicroRNAs, as their name suggests, are tiny bits of genetic material. Instead of being translated into proteins like many RNAs, microRNAs act to regulate gene expression—acting like a dimmer switch on a light.

In humans there are almost 2,000 distinct microRNAs, which collectively regulate somewhere between 30 and 80 percent of human genes.

Despite their ubiquity, their importance has become evident only in the last decade or so, and details are still emerging. Davis noted a host of critical questions remain: How complex is the microRNA regulatory landscape for neural circuits mediating essential behaviors? To what extent are microRNA mechanisms used in the brain? Do they regulate distinct sets of target genes in different cell types and/or developmental stages?

The new collaborative study will use Drosophila, the common fruit fly, which is a widely recognized substitute for human memory studies, to help answer some of these questions. The number of the grant is 1P01NS090994.

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**Scripps Florida Scientists Predict Cell Changes that Affect Breast Cancer Growth, Opening Door to More Effective Therapies**

JUPITER, FL – April 28, 2016 – Designing effective new drugs, especially drugs to fight cancer, demands that you know as much as you can about the molecular workings of cancer growth. Without that, it’s like planning to fight a war against an enemy you’ve never seen.

Using a broad spectrum of analytical tools, scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown how sometimes small, often practically imperceptible, structural changes in a key breast cancer receptor are directly linked to regulating molecules and can produce predictable effects in curbing or accelerating cancer growth.
This predictive statistical approach, published recently in the journal *Molecular Systems Biology*, moves science one step closer to the development of more effective structure-based drug design to treat the disease.

“Our long-term goal,” said team leader Kendall Nettles, an associate professor at TSRI, “is to be able to predict proliferative or anti-proliferative activity of receptor molecule complexes by identifying structural changes that lead to specific outcomes. In many cases, we can identify structural features that could help guide more effective drug development.”

To identify the root of estrogen receptor (ERα) cell signaling that drives breast cancer cell proliferation, Nettles and his colleagues synthesized more than 240 estrogen receptor binding molecules (“ligands”) that led the cancer to proliferate, using structural analysis to determine the basis for receptor activity.

Many current drugs target signaling proteins like the estrogen receptor. For example, the drug tamoxifen (Nolvadex®, AstraZeneca) blocks the estrogen receptor’s proliferative effects of naturally occurring estrogen in breast cancer cells, but can increase the risk of uterine cancer.

Research Associate Sathish Srinivasan, a co-first author of the study with Research Associate Jerome Nwachukwu, pointed out the new research suggests that certain structural changes might be made to the binding pocket to eliminate this negative side effect. “Drugs like tamoxifen can have different effects in different tissues because of structural changes often not discernable using traditional methods,” Srinivasan said. “Our approach reveals some mechanisms associated with tissue specificity and several predictive structural features.”

To further test these signaling models, the team solved the atomic structure of some 76 different estrogen receptor-ligand complexes to better understand these responses.

“We can predict some of these effects by measuring the distance between two specific carbon atoms of the estrogen receptor,” said Nwachukwu.

Nettles concluded, “This is the first time we have been able to use these atomic structures to identify how very small changes from the ligands give different outcomes, leading us towards the goal of predicting which ligands are going to make the most effective treatments for breast cancer.”

In addition to Nettles, Nwachukwu and Srinivasan, authors of the study, “Predictive Features of Ligand-Specific Signaling through the Estrogen Receptor,” include Hai-Bing Zhou, Yangfan Zheng, Song Wang, Chune Dong and Zongquan Liao of Wuhan University (China); Jason Nowak and Nicholas J. Wright of TSRI; René Houtman of PamGene International (The Netherlands); Kathryn E. Carlson, John A. Katzenellenbogen and Jian Min of the University of Illinois; Jatinder S. Josan of Virginia Tech; and Olivier Elemento of Weill Cornell Medical College.

The work was supported by the National Institutes of Health (PHS 5R37DK015556, 3R33CA132022 and 5R01DK077085), Frenchman’s Creek Women for Cancer Research,
Scripps Florida Awarded $2.5 Million to Advance Development of RNA-Based Therapeutics

JUPITER, FL – May 4, 2016 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have been awarded a $2.5 million grant from the National Institute of General Medical Sciences of the National Institutes of Health to design precision drug candidates that target disease-associated RNAs.

Matthew Disney, a TSRI professor, will be the principal investigator for the new four-year study.

“A major goal of genome sequencing efforts is to develop drug targets that could enable the development of patient-specific therapies,” Disney said. “In this project, we are developing quick ways to convert this information into lead drugs by using several novel and transformative technologies we developed. The new grant will keep us moving forward and allow us to tackle many new challenges in the area of precision medicine.”

While to date large macromolecules have generally been used to target RNA, small molecules can pass through the blood-brain barrier, a critical factor in the treatment of neurological diseases and cancer that affects the brain.

The Disney lab’s untraditional approach has been broadly applicable in developing precision probes to target disease-causing RNA repeat expansions, which cause more than 30 diseases—including Huntington’s, which has no cure—affecting millions worldwide.

Disney’s successful efforts in identifying various drug-like small molecules that bind to RNA is the result of his lab’s broad, bottom-up, computational approach known as Inforna, which can deep mine information against such genome sequences and cellular RNAs.

The new grant will enable Disney and his team to further investigate the manipulation of microRNAs. Discovered only in the 1990s, microRNAs are short molecules that work within virtually all animal and plant cells. Typically, each one functions as a “dimmer switch” for one or more genes, binding to the transcripts of those genes and effectively keeping them from being translated into proteins.

The new grant will also allow Disney to expand development of small molecules that target two miRNAs with a single small molecule and to study the cellular consequences targeting multiple disease pathways using what he calls a “designer poly-pharmacy approach.” The number of the grant is 2R01GM097455-05.
A Drug Candidate Successfully Targets Cancer-Causing RNA

JUPITER, FL – May 9, 2016 – In a development that could lead to a new generation of drugs to precisely treat a range of diseases, scientists from the Florida campus of The Scripps Research Institute (TSRI) have for the first time designed a drug candidate that decreases the growth of tumor cells in animal models in one of the hardest to treat cancers—triple negative breast cancer.

“This is the first example of taking a genetic sequence and designing a drug candidate that works effectively in an animal model against triple negative breast cancer,” said TSRI Professor Matthew Disney. “The study represents a clear breakthrough in precision medicine, as this molecule only kills the cancer cells that express the cancer-causing gene—not healthy cells. These studies may transform the way the lead drugs are identified—by using the genetic makeup of a disease.”

The study, which the journal Proceedings of the National Academy of Sciences is publishing online ahead of print during the week of May 9, 2016, demonstrates that the Disney lab’s compound, known as Targaprimir-96, triggers breast cancer cells to kill themselves via programmed cell death by precisely targeting a specific RNA that ignites the cancer.

Short-Cut to Drug Candidates

While the goal of precision medicine is to identify drugs that selectively affect disease-causing biomolecules, the process has typically involved time-consuming and expensive high-throughput screens to test millions of potential drug candidates to identify those few that affect the target of interest. Disney’s approach eliminates these screens.

The new study uses the lab’s computational approach called Inforna, which focuses on developing designer compounds that bind to RNA folds, particularly microRNAs.

MicroRNAs are short molecules that work within all animal and plant cells, typically functioning as a “dimmer switch” for one or more genes, binding to the transcripts of those genes and preventing protein production. Some microRNAs have been associated with diseases. For example, microRNA-96, which was the target of the new study, promotes cancer by discouraging programmed cell death, which can rid the body of cells that grow out of control.

In the new study, the drug candidate was tested in animal models over a 21-day course of treatment. Results showed decreased production of microRNA-96 and increased programmed cell death, significantly reducing tumor growth. Since targaprimir-96 was highly selective in its targeting, healthy cells were unaffected.

In contrast, Disney noted, a typical cancer therapeutic targets and kills cells indiscriminately, often leading to side effects that can make these drugs difficult for patients to tolerate.
“In the future we hope to apply this strategy to target other disease-causing RNAs, which range from incurable cancers to important viral pathogens such as Zika and Ebola,” added Research Associate Sai Pradeep Velagapudi, the first author of the study and a member of the Disney lab.

In addition to Disney and Velagapudi, authors of the study, “Design of a Small Molecule Against an Oncogenic Non-coding RNA,” were Michael D. Cameron, Christopher L. Haga, Laura H. Rosenberg, Marie Lafitte, Derek Duckett and Donald G. Phinney of TSRI. The work was supported by the National Institutes of Health (R01GM9455) and The Nelson Fund for Therapeutic Development.

Scripps Florida Scientists Design Potent Therapeutic 'Warheads' That Target Cancer Cells

JUPITER, FL – May 9, 2016 – In a pair of related studies, chemists from the Florida campus of The Scripps Research Institute (TSRI) have identified and designed dozens of molecular “warheads” that not only can detect a key biomarker of cancer, but also could be developed into a potent new class of drug candidates for a range of diseases.

A number of these molecules are already “hidden” in drugs approved by the U.S. Food and Drug Administration (FDA), raising the possibility that these widely used pharmaceuticals could be made even more effective using more potent/selective covalent inhibitors or “warheads.”

The studies, which were published recently in the journals Chemical Science and Chemical Communication, were led by TSRI Associate Professor Kate Carroll.

The molecules in question are known as “nucleophiles” (literally, nucleus lovers), which share their electrons with “electrophiles” (literally, electron lovers) and serve as their atomic dance partners. This sharing of electrons creates an interaction known as a covalent bond, which some consider the fundamental basis of chemical reactivity.

Electrophiles have been available to the scientific community for decades for use as tools to probe levels of cysteine sulfenic acid—a marker for cancer and other diseases—and to install as “warheads” or covalent modifiers in drugs that target high levels of sulfenic acid in cells.

The downside of electrophiles is that they compete with high concentrations of off-target nucleophiles in the cell, such as glutathione. In addition, this class of covalent inhibitors indiscriminately targets the protein in healthy and diseased cells. “To counteract this effect, our complementary approach would use nucleophile ‘warheads’ attached to a binding scaffold that would target sulfenic acid on therapeutically important proteins in unhealthy cells under oxidative stress,” said Carroll.

To produce a library of “designer” nucleophiles with far greater reactivity, Carroll and her colleague, Senior Research Associate Vinayak Gupta, developed a unique screen. So far, some of the nucleophiles they identified possess more than 200 times the current standard for sulfenic acid probes.
“We now have about 150 of these ‘warheads’ in our library,” Carroll said.

While the greater interest in the scientific community has been in electrophiles, the TSRI team also examined previously unidentified nucleophilic functional groups, such as those within the Pfizer rheumatoid arthritis drug tofacitinib (XELJANZ®).

“The nucleophiles we identified in this study represent the first covalent strategy to target sulfenic acid that should be highly enabling for the drug discovery community,” Gupta said. “Moreover, our findings that tofacitinib reacts robustly with sulfenic acid shows that ‘warheads’ or other functional groups in these drugs may indeed have new or alternative mechanisms of action.”

Carroll added, “Tofacitinib may have multiple modes of action that include a nucleophile targeting cysteine sulfenic acid in the active site of JAK kinases. If the nucleophile contributes positively to therapeutic outcome, it might be possible to optimize that chemical property and make the drug more effective.”

Carroll says she uncovers more instances of nucleophiles “hidden in plain sight” every day, suggesting that nucleophiles may, in fact, be unsung central players in these reactions.

The studies, “Profiling the Reactivity of Cyclic C-Nucleophiles towards Electrophilic Sulfur in Cysteine Sulfenic Acid,” and “Rational Design of Reversible and Irreversible Cysteine Sulfenic Acid-Targeted Linear C-Nucleophiles,” were published in Chemical Science and Chemical Communications, respectively.

The work was supported by the National Institutes of Health (grant numbers R01 GM102187 and R01 CA174864).

**Scripps Florida Scientists Show Commonly Prescribed Painkiller Slows Cancer Growth**

JUPITER, FL – May 25, 2016 – Scientists from the Florida campus of The Scripps Research Institute (TSRI) have found that one of the most widely prescribed pain and anti-inflammation drugs slows the growth rate of a specific kind of cancer in animal models and suggests the medication could have the same effect on other types of tumors.

The new study, published online ahead of print by the journal Cancer Research, focused on the effects of celecoxib (Pfizer’s Celebrex®).

Celebrex® targets an enzyme called “cyclooxygenase-2” (COX-2), which is linked to pain and inflammation. This enzyme is also critical in the creation of prostaglandins, compounds that act like hormones and play a role in promoting tumor growth. COX-2 expression is typically low in normal tissue, but high in multiple types of cancers.
“We were actually interested in determining what a particular signaling pathway does in cancer,” said TSRI Associate Professor Joseph Kissil, who led the study. “In the process, we found that it activates genes that promote survival of tumor cells and that they do so by turning on enzymes involved in inflammation, including COX2, which anti-inflammatory drugs like Celebrex® inhibit.”

The researchers went on to conduct animal studies tracking the effects of celecoxib on the growth of cancer cells from a tumor type known as neurofibromatosis type II (NF2). In humans, NF2 is a relatively rare inherited form of cancer caused by mutations in the anti-tumor gene NF2, which leads to benign tumors of the auditory nerve.

Animals received a daily dose of the drug, and tumor growth was followed by imaging. Analysis of the results showed a significantly slower tumor growth rate in celecoxib-treated models than in controls.

Using various approaches, the new study also showed that a signaling cascade known as the Hippo-YAP pathway is involved in these results and that the protein YAP is required for the proliferation and survival of NF2 cells and tumor formation.

“Our study shows that COX2 inhibitors do have an effect on the tumor cells,” said TSRI Research Associate William Guerrant, the study’s first author. “They also have an impact on inflammatory responses that play a role in tumor growth. It’s possible that in other cancers these effects might actually be stronger because of the drug’s impact on inflammation.”

In addition to Kissil and Guerrant, other authors of the study, “YAP Mediates Tumorigenesis in Neurofibromatosis Type 2 by Promoting Cell Survival and Proliferation through a COX-2–EGFR Signaling Axis,” are Smitha Kota, Scott Troutman, Vinay Mandati and Mohammad Fallahi of TSRI; and Anat Stemmer-Rachamimov of Massachusetts General Hospital.

The work was supported by the National Institutes of Health (grants NS077952 and CA124495). Guerrant is also a recipient of a Young Investigator Award from the Children’s Tumor Foundation.

**Scripps Florida Scientists Create Compound that Erases Disease-Causing RNA Defects**

JUPITER, FL – June 1, 2016 – In an important new study with implications for the treatment of dozens of incurable diseases, scientists from the Florida campus of The Scripps Research Institute (TSRI) have for the first time created a drug candidate that attacks and neutralizes the RNA structure that causes an incurable progressive, inherited disease involving a gradual loss of control over body movement.

The study, which was published June 1, 2016 in *Nature Communications*, showed the compound significantly improved several aspects of cells taken directly from patients with spinocerebellar ataxia type 10 (SCA10), a form of spinocerebellar ataxia.
“More than 30 diseases, all of them incurable, are caused by RNA repeats,” said TSRI Professor Matthew Disney, who led the study. “By a thorough basic science investigation, we identified small molecules that target RNA base pairs precisely. We then leveraged this information to design the first drug candidate that binds to disease-causing defects in SCA10. Application of the drug candidate returns certain aspects of those cells to healthy levels—it’s like the defect is not even there.”

SCA10 is caused by what is called a pentanucleotide repeat (a genetic sequence of five nucleotides repeated many more times than normal) affecting the mitochondria, the cell’s energy source. The new drug candidate, known as 2AU-2, targets these repeats by binding to RNA base pairs.

“The potent bioactivity of 2AU-2 to moderate the structurally induced toxicity in SCA10 strongly suggests that base-pair-targeting RNA modules could have broad applicability in our effort to develop other compounds that target different RNAs,” said TSRI Research Associate Wang-Yong Yang, the first author of the study. “More than 70 percent of RNA secondary structure is made up of base pairing.”

The Disney group has developed new tools to identify optimal interactions between RNA structures and drug candidates targeting them. A database of these interactions has already been used to design several small molecule drug candidates.

“We are in the process of developing tools that allow one to design small molecules to target any RNA structural motif in a complex cellular environment. That environment can contain millions of other RNAs. In this study, Wang-Yong has done an exceptional job tackling this previously-thought-to-be-impossible molecular recognition problem,” Disney said.

Pathogenic RNA repeats contribute to disorders including Huntington’s disease, fragile X-associated tremor ataxia syndrome and myotonic dystrophy type 1 and 2.

In addition to Disney and Yang, other authors of the study, “Studying Small Molecule Recognition of RNA Base Pairs Enables Design of a Bioactive Small Molecule that Targets r(AUUCU) Repeats in Spinocerebellar Ataxia 10,” are Mark Southern of TSRI and Rui Gao and Partha S. Sarkar of the University of Texas Medical Branch.

The work was supported by the National Institutes of Health (R01 GM097455 and DP1NS096898), the John Sealy Memorial Endowment Fund for Biomedical Research, the FRAXA Research Foundation and TSRI.

Skaggs Family Gives $2 Million for New TSRI Graduate Program Endowment

JUPITER, FL – June 2, 2016 – The Skaggs family has given a new $2 million gift to support exceptional students in The Scripps Research Institute (TSRI) graduate program.

“I would like to thank members of the Skaggs family for their remarkable generosity, which has had a transformative effect on this institution,” said TSRI CEO Peter Schultz. “This new
endowment, which brings the family’s total gifts to TSRI to approximately $131 million, will help us continue to recruit the best students for advanced training at the intersection of biology and chemistry. In so doing, the gift also benefits our faculty, whose research programs will be enhanced by the efforts of these outstanding fellows.”

The new gift was made through the Skaggs family’s foundation, The ALSAM Foundation.

“I am delighted that members of the ALSAM grants committee, including TSRI Trustees Claudia Skaggs Luttrell and Mark Skaggs, have chosen to support the training of the next generation of scientists who will forge new ground in medicine and drug discovery,” said TSRI President Steve Kay. “I would like to express my deep appreciation for this support.”

Luttrell added, "At the ALSAM Foundation, we carry on the legacy of my parents’ belief in the importance of education and medical research for the betterment of humankind. We hope this gift will fulfill this philosophy by training the next generation of scientists, while contributing to the scientific knowledge that underpins new therapeutic discoveries.”

Beginning this fall, one exceptional member of the entering class will be selected by the TSRI admissions committee to be designated as a Skaggs Fellow.

The Skaggs Fellow’s first-year stipend will be paid from the new endowment funds. In addition, in subsequent years of study, the student will receive a research supplement of up to $5,000.

For more information on TSRI’s graduate program, which is consistently ranked among the top 10 in the nation in its fields of chemistry and biology, see the Education web pages.

Scripps Florida Scientists Discover a New Protein Crucial to Normal Forgetting

JUPITER, FL – June 2, 2016 – When Elvis released his first number-one country hit “I Forgot to Remember to Forget” in 1955, the song was more correct scientifically than he could have imagined. Humans need to forget as part of the brain’s system for the management of memories acquired across a lifetime.

“Understanding the process of forgetting could have an enormous impact on how we treat a whole range of diseases,” said Ron Davis, chair of the Department of Neuroscience on the Florida campus of The Scripps Research Institute (TSRI). “Certain memories are intrusive and, with sufficient knowledge of how the brain forgets, we should be able to remove selective memories. Alternatively, we could find a way to inhibit forgetting in those suffering from memory disorders such as Alzheimer’s disease.”

The new study, published June 2, 2016 online ahead of print by the journal Neuron, uncovers a new aspect of how this process works. The results show that a protein called “Scribble” orchestrates the intracellular signaling processes for forgetting, joining several molecules to forge a pathway.
To conduct this research, Davis and his colleagues turned to *Drosophila*, or the common fruit fly, a critical model for studying memory found to be highly applicable to humans.

By “knocking down” the expression of the gene that produces Scribble, the researchers produced flies that were able to remember twice as much as normal flies, simply because they failed to forget at the normal rate. The researchers also identified Scribble’s crucial role in interacting with other key molecular players for forgetting within the fly brain.

“What Scribble does is combine the Rac1 and dopamine pathways together into a single dynamic pathway that controls active forgetting,” Davis said. “It orchestrates a series of molecules that are involved in this particular forgetting pathway, and there may well be others we have yet to discover.”

“The Scribble protein is expressed in the same neurons that encode olfactory memories,” said TSRI Senior Staff Scientist Isaac Cervantes-Sandoval, the study’s first author. “We were able to show that it regulates memory by involvement in this particular forgetting pathway, an important biological process that has been surprisingly ignored.”

In addition to Davis and Cervantes-Sandoval, other authors of the study, “Scribble Scaffolds a Signalosome for Active Forgetting,” are Molee Chakraborty and Courtney MacMullen of TSRI.

This work was supported by the National Institutes of Health (grants 2R37NS19904 and 2R01NS05235).

**Scripps Florida Chemist Named Finalist for Blavatnik Awards**

JUPITER, FL – June 3, 2016 – Matthew Disney, professor on the Florida campus of The Scripps Research Institute (TSRI), has been named a chemistry finalist for the 2016 Blavatnik National Awards for Young Scientists.

The awards, established by the Blavatnik Family Foundation and administered by the New York Academy of Sciences, recognize outstanding faculty-rank researchers from the nation's leading academic and research institutions.

“The 2016 National Finalists in Chemistry are performing revolutionary research that has the potential to improve lives around the globe,” noted the Blavatnik Family Foundation and New York Academy of Sciences in a statement.

Disney’s research focuses on RNA-based drug discovery. His lab’s goal is to create new tools for the development of therapies based on a patient’s individual genome sequence and the RNA products of those genes. With these tools, Disney and his team are currently targeting rare “orphan” diseases with no known cure and more common disorders that show poor prognoses, such as drug-resistant cancers.
“Every step of our science has a new challenge along the way,” said Disney. “Given that the diseases that we work are often times incurable, we are always motivated to continue to advance our compounds to therapeutic efficacy and then on to patients.”

Another TSRI scientist, Phil Baran, Darlene Shiley Professor of Chemistry on the Scripps California campus, was also nominated as a Blavatnik Awards finalist. Baran’s lab explores new avenues for the efficient and practical construction of organic molecules, both naturally occurring and man-made, by pursuing longstanding synthetic challenges and by designing methods of broad utility.

Disney and Baran will be honored at an awards ceremony on September 12 at the American Museum of Natural History in New York City.

For more information on Disney and his research, see his faculty webpage and lab website.